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# BMJ Open

## The effect of community-directed treatment with ivermectin on the prevalence and incidence of epilepsy in an onchocerciasis endemic area of Tanzania: a study protocol

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3 1 **The effect of community-directed treatment with ivermectin on the prevalence and**  
4 **incidence of epilepsy in an onchocerciasis endemic area of Tanzania: a study protocol**  
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## 17 **ABSTRACT**

### 18 **Introduction**

19 Worldwide, there are an estimated 50 million people affected by epilepsy. Its etiology is manifold,  
20 and parasitic infections play an important role, specifically onchocerciasis. In Tanzania, Uganda  
21 and South Sudan a distinctive form of epilepsy has been described as nodding syndrome (NS),  
22 affecting mainly children and causing nodding seizures, mental retardation and debilitating  
23 physical development. NS is only described from onchocerciasis endemic areas.

24 Onchocerciasis is treatable with ivermectin. Control programs using community directed  
25 treatment with ivermectin (CDTi) are implemented in endemic countries. This study is designed  
26 to test whether the implementation of CDTi decreases the incidence of epilepsy and NS in  
27 onchocerciasis endemic regions.

### 28 **Methods and analysis**

29 The study will be conducted in the Mahenge highlands in Tanzania. Study site selection is based  
30 on an in-depth study on epilepsy in that area dating from 1989. CDTi was introduced in 1997. By  
31 a door-to-door approach, the population will be screened using a validated questionnaire to  
32 identify suspected epilepsy cases. Suspected cases are invited for to neurological examination  
33 for case verification. Additionally, ivermectin use will be assessed at household level. Data will be  
34 analysed in comparison to the 1989 data to reveal pre- and post-CDTi implementation  
35 prevalence and incidence of epilepsy.

### 36 **Ethics and dissemination**

37 This study has obtained ethical approval from the relevant ethics committees in the countries. It  
38 will contribute to a better understanding of the linkage between the onset of epilepsy and NS in  
39 particular, onchocerciasis and CDTi. Comparing the epidemiological data on epilepsy from pre-  
40 CDTi and 20 years after its introduction will allow identifying a potential protective effect of  
41 ivermectin on the onset of epilepsy. Results and lessons learned will be published in peer-

1  
2  
3 42 reviewed journals, presented at scientific conferences and to the health authorities in Tanzania,  
4  
5 43 and are of relevance for other regions where onchocerciasis associated epilepsy occurs.  
6  
7 44

8  
9 45 **Strengths and limitations of this study:**

- 10  
11 46 • This study will be carried out in an onchocerciasis endemic area of Tanzania, where nodding  
12  
13 47 syndrome (NS) has been described for the first time and will allow comparison of large scale  
14  
15 48 population based data on epilepsy epidemiology pre- and 27 years post-CDTi.  
16  
17  
18 49 • Answers key questions of the impact of community directed treatment with ivermectin (CDTi)  
19  
20 50 targeting onchocerciasis and its potential preventive effect on epilepsy, and specifically  
21  
22 51 nodding syndrome.  
23  
24 52 • Bridging expertise on infectious diseases (onchocerciasis control) and chronic diseases  
25  
26 53 (epilepsy) through the close collaboration of experts in both fields.  
27  
28  
29 54 • Pre-CDTi epilepsy surveys in Tanzania dates from 1989 and adjusting for potential  
30  
31 55 confounding factors other than CDTi that may influence epilepsy incidence and prevalence in  
32  
33 56 the area need to be carefully assessed.  
34  
35 57 • Slightly differing methodology might limited the potential to compare data, and focus on  
36  
37 58 villages with high epilepsy burden in the past may lead to an overestimation of the effect of  
38  
39 59 CDTi.  
40

41 60  
42  
43 61 **Key words**

44  
45 62 Epilepsy

46  
47 63 Nodding disease

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49 64 Onchocerciasis

50  
51 65 Ivermectin

52  
53 66 Tanzania  
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56 67

## 68 INTRODUCTION

69 Epilepsy is a chronic disease estimated to affect 50 million people worldwide according to World  
70 Health Organisation (WHO) [1]. In general, higher prevalence and incidence is reported from  
71 those populations living in low and middle income countries (LMICs) when compared to  
72 industrialized countries [2, 3]. In fact, more than 85% of the global burden of epilepsy occurs in  
73 those 49% of the global population living in LMICs [4, 5]. The etiology of epilepsy is very diverse  
74 and not yet fully understood. Besides birth trauma and head injury involving the brain, also  
75 infections can trigger epilepsy. Specifically parasitic infections are in the focus and those most  
76 described as associated with the onset of epilepsy are cerebral malaria, neurocysticercosis,  
77 echinococcosis, and onchocerciasis [6, 7]. Many of these epilepsy cases could be prevented  
78 through timely anti-parasitic treatment. Epilepsy manifests in a variety of seizure types and  
79 degrees of intensity [8]. In Tanzania, Uganda and South Sudan, a distinct form of epilepsy has  
80 been described as nodding syndrome (NS) [9, 10]. NS is a debilitating epileptic encephalopathy  
81 mainly affecting children at the ages of 3 and 18 years [11]. The seizures are characterized by a  
82 brief loss of muscle-tone in the neck, leading to repetitive head-nodding [12]. In contrast to other  
83 forms of epilepsy, cognitive decline, retardation in cognitive development, and stunted growth in  
84 formerly normally developing children are also associated with the disease [13]. So far, NS is  
85 solely described from onchocerciasis endemic areas [10]. Since its first description from  
86 Tanzania in the 1960s [9] until the mid-1990s, NS was a rare condition with single cases reported  
87 predominantly in African countries [14]. Since, an NS epidemic has been observed in the past  
88 two decades in northern Uganda [15] and in neighboring South Sudan [13]. The weight of the  
89 public health burden caused by NS can be illustrated by the situation in the West Equatorial State  
90 in South Sudan, where in the village of Mvolo in South Sudan, over 50% of the families had at  
91 least one child affected by epilepsy of the NS type, resulting in one in six children of the village  
92 suffering from epilepsy [16].

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3 93 Health systems services in remote rural regions in Africa are rarely capable to provide continuous  
4  
5 94 anti-epileptic treatment to those patients in need [5]. Further more, most health care workers lack  
6  
7 95 training to diagnose and treat persons with epilepsy adequately. The costs associated to seeking  
8  
9 96 professional care by a trained doctor or a neurologist in a major city can often not be afforded by  
10  
11 97 epileptic patients and their families from rural areas. In many societies in Africa, and in addition to  
12  
13 98 the clinical burden, epilepsy is perceived as a possession by evil spirists and hence bears a  
14  
15 99 stigma that puts the whole family of a diseased individual at risk for social isolation [17].  
16  
17 100 Moreover, the family's economy is negatively impacted by the disease, since an epileptic family  
18  
19 101 member needs specific care and supervision, detaining care takers from their subsistence duties  
20  
21  
22 102 [18].  
23

24 103 Many hypotheses on the etiology of NS, and epilepsy in general, have been raised but currently,  
25  
26 104 the causing mechanism is still not fully understood [15]. Several studies have shown  
27  
28 105 epidemiological association of epilepsy with parasitic infections, for NS particularly  
29  
30 106 onchocerciasis [7, 19, 20]. NS is only known to occur in some onchocerciasis endemic areas,  
31  
32 107 and case-control studies have demonstrated a statistically significant higher prevalence of  
33  
34 108 onchocerciasis in individuals with NS than in controls [13, 15]. It is, however, unclear how  
35  
36 109 onchocerciasis might cause NS [20]. Although the eye and the optical nerve are affected when  
37  
38 110 onchocerciasis causes blindness, microfilariae and adult *Onchocerca volvulus* (OV) worms are  
39  
40 111 not generally considered able to invade the central nervous system. Recent research  
41  
42 112 hypothesises that an immunological cross-reaction of onchocerciasis-specific antibodies may  
43  
44 113 provoke a neurotoxic reaction and trigger NS [21].  
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49 115 **Onchocerciasis, a treatable neglected tropical disease facing obstacles on the road to**  
50  
51 116 **elimination**  
52

53 117 Onchocerciasis is a parasitic disease caused by an infection with the the worm *Onchocerca*  
54  
55 118 *volvulus* whose filarial larvae are transmitted by blackflies (*Simuliidae* spp.). In the final host,  
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3 119 humans, the adult female worms encapsulate in the subcutaneous tissue forming visually  
4  
5 120 detectable nodules. Each female worm releases up to one thousand microfilariae per day. These  
6  
7 121 microfilariae provoke itching, dermatitis and – if left untreated – blindness, which led to the  
8  
9 122 disease also being called river blindness. Blackflies get infected with microfilariae when biting  
10  
11 123 infected humans in proximity to fast flowing rivers, the breeding site of the blackflies. After  
12  
13 124 passing through several larval stages, infected blackflies spread the parasite by biting other  
14  
15 125 people. Onchocerciasis is treatable with ivermectin, a drug with high efficacy and close to nil  
16  
17 126 adverse effects [22]. The drug has a twofold mechanism of action: (i) it kills the microfilariae and  
18  
19 127 (ii) it inhibits their release by the adult female worm for up to two years after a single dose  
20  
21 128 treatment [23]. Hence, ivermectin has a strong impact on reducing transmission. However,  
22  
23 129 ivermectin is not lethal to adult worms and infected persons have to take it annually for up to 15  
24  
25 130 years, until all the adult worms die [24]. Onchocerciasis is a priority disease scheduled for  
26  
27 131 elimination by 2025 by the WHO [1]. Today, 99% of the globally 37 million people infested live in  
28  
29 132 Africa [1]. In 1995, the African Program for Onchocerciasis Control (APOC) was initiated for the  
30  
31 133 implementation of the onchocerciasis control programme based on community directed treatment  
32  
33 134 with ivermectin (CDTi). APOC was coordinating this activities in endemic areas of 22 African  
34  
35 135 countries [25]. Since May 2016, CDTi control programmes are integrated in the WHO Expanded  
36  
37 136 Special Project for Elimination of Neglected Tropical Diseases (ESPEN) [26]. CDTi overcomes  
38  
39 137 the limited performance of weak health systems in rural areas by using an active, strategic  
40  
41 138 involvement of the community [27]. To reach the entire population, ivermectin distribution is  
42  
43 139 organized by trained volunteers in each village, resulting in a large geographical coverage. CDTi,  
44  
45 140 in certain regions combined with the control of the blackfly by larviciding of breeding sites (i.e.  
46  
47 141 fast flowing rivers), resulted in a measurable impact reflected by a remarkable transmission  
48  
49 142 reduction in the past 20 years [28]. But success and effectiveness of these targeted interventions  
50  
51 143 lack comprehensiveness. Certain onchocerciasis endemic regions remain undersupplied or  
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53 144 unreachable for CDTi due to political instability, insecurity or armed conflicts [29]. As a  
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3 145 consequence in the war-affected regions of South Sudan and northern Uganda, onchocerciasis  
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5 146 control measures were stopped or implementation started only recently. Moreover,  
6  
7 147 misconceptions and the fear of adverse effects result in suboptimal therapeutic coverage and  
8  
9 148 reduce the effectiveness of control programs [30]. Adding to the complexity of onchocerciasis  
10  
11 149 control, in regions where *Loa loa* and onchocerciasis are co-endemic, ivermectin may cause  
12  
13 150 severe adverse effects (encephalopathy, coma or death) in *Loa loa* infected individuals with high  
14  
15 151 microfilariae load [31, 32]. Thus, CDTi implementation in such regions requires additional  
16  
17 152 precautions [33]. This is the case in certain regions of Cameroon and the DRC [34]. Compliance  
18  
19 153 to CDTi programs can also decrease over the years since less direct positive effects can be  
20  
21 154 observed when onchocerciasis prevalence drops, and healthy feeling people may not appreciate  
22  
23 155 the importance of continuing repeated drug treatment [35].  
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## 28 157 **The potential of CDTi to reduce the incidence of epilepsy in onchocerciasis endemic** 29 30 158 **regions**

31  
32 159 The endemicity of onchocerciasis and the prevalence and incidence of epilepsy are influenced by  
33  
34 160 a multitude of factors (Figure 1). These factors are of uncontrollable nature (climate,  
35  
36 161 environment, ecology), and of controllable nature (prevention and intervention programs, access  
37  
38 162 to health care and treatment). The controllable factors can be addressed. i.e. onchocerciasis  
39  
40 163 cases can be cured and new onchocerciasis associated epilepsy (OAE) cases prevented.  
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45 165 <<<<<<Figure 1 near here>>>>>>>>

46  
47 166  
48  
49 167 An epidemiological association between epilepsy and onchocerciasis was first documented by  
50  
51 168 Boussinesq *et al.* (2002) in a case-control study performed in 1991-92 in the Mbam valley in  
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53 169 Cameroon [20]. This study demonstrated a significantly higher microfilarial load in persons with  
54  
55 170 epilepsy than in controls. During the past 25 years, study results from further onchocerciasis-

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3 171 endemic African countries underline this association [19, 36]. Case-control studies in northern  
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5 172 Uganda and South Sudan produced similar results, showing a higher prevalence of  
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7 173 onchocerciasis in NS cases compared to non-epileptic controls [13, 15]. Both areas were - and  
8  
9 174 South Sudan still is - affected by armed conflicts. In 2012, after the conflict ended in northern  
10  
11 175 Uganda, the NS epidemic was investigated. Following on, epilepsy treatment was provided [37],  
12  
13 176 biannual CDTi was implemented and larviciding of major rivers was carried out. Since 2013 the  
14  
15 177 NS epidemic in northern Uganda has reportedly been halted, although the situation has not yet  
16  
17 178 been empirically assessed [38]. In contrast in South Sudan, where CDTi was stopped because of  
18  
19 179 insecurity, new cases of NS continue to appear [16]. Based on the observations from northern  
20  
21 180 Uganda, it has been suggested that ivermectin may reduce the incidence of NS and other forms  
22  
23 181 of epilepsy in onchocerciasis endemic areas [39]. Considering that 30% of the globally 37 million  
24  
25 182 individuals infected with onchocerciasis do not have access to effective treatment [1], and that  
26  
27 183 1% of those develop epilepsy (equivalent to the estimated excess prevalence of epilepsy over  
28  
29 184 non-onchocerciasis areas) [7], the number of excess cases of epilepsy attributed to  
30  
31 185 onchocerciasis could exceed 100'000. It is hypothesized that with annual administration of  
32  
33 186 ivermectin these cases are preventable.

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36  
37 187 Recent observations in the DRC, and northern Uganda suggest that optimal coverage of  
38  
39 188 ivermectin as an onchocerciasis control intervention, may stop the incidence of NS and other  
40  
41 189 forms of OAE [39].

42  
43 190 In Tanzania, Morogoro region is among the five regions where onchocerciasis is endemic. The  
44  
45 191 region presents four foci: Uluguru mountain, Ulanga/Mahenge, Kilosa and the Nguru mountain  
46  
47 192 focus [40]. The Ulanga district, specifically the Mahenge area, was known for its high endemicity  
48  
49 193 of onchocerciasis since the early last century [41]. Mass drug administration (MDA) using CDTi  
50  
51 194 on annual bases as recommended by WHO for elimination of onchocerciasis was introduced in  
52  
53 195 the Mahenge area in 1997 [42]. Before CDTi was implemented, onchocerciasis prevalence in the  
54  
55 196 area was estimated at 69% [25]. During the last rapid epidemiological mapping of onchocerciasis

197 (REMO) in 10 villages during 2008/2009, onchocerciasis prevalence was estimated at 20.3%  
198 [43].

199  
200 **Epilepsy in the Mahenge area, Tanzania**  
201 In the 1960s, Aall-Jilnek was the first to report a high burden of epilepsy in the Mahenge area,  
202 and also described the first NS cases [9]. In 1989, Rwiza et al. carried out a population based  
203 survey to determine prevalence and incidence of epilepsy in the Ulanga district and found an  
204 annual incidence of 73.3 new cases in 100 000. The prevalence was 10.2 cases in 1000, and  
205 varied between villages from 5.1 to 37.1 cases in 1000. Those villages with the highest  
206 prevalence were located in the Mahenge highlands (Table 1) [44].

207  
208 **Table 1. Population size and prevalence of epilepsy in those villages of the Ulanga district,**  
209 **Tanzania, showing the highest prevalence in 1989, as reported by Rwiza et al. in 1992**

Name of Village	Population size	Number of Epilepsy cases	Prevalence per 1000 people
Sali <sup>δ</sup>	1282	14	10.9
Mdindo <sup>δ</sup>	539	20	37.1
Vigoj <sup>δ</sup>	1822	23	12.6
Lupiro	1697	17	10
Misegezi	1667	18	10.8
<b>Total</b>	<b>7007</b>	<b>92</b>	<b>13.13</b>

210 <sup>δ</sup>Located in Mahenge highlands

211  
212 Numberless rivers and streams have their source in the Mahenge highlands, and these provide  
213 breeding sites for the blackfly, the intermediate host of *Onchocerca volvulus*.

## 214 **Goal**

215 This study aims at investigating the effect of CDTi for the treatment and prevention of  
216 onchocerciasis on the incidence of epilepsy and NS. Bearing the association of onchocerciasis

217 and epilepsy in mind, it is expected that, since the onchocerciasis interventions have been  
 218 launched, the prevalence of epilepsy has diminished and the incidence has decreased  
 219 accordingly. If CDTi for onchocerciasis control has an effect on the onset of epilepsy and NS, it is  
 220 expected to observe an age shift in epilepsy cases when compared to the study from 1989 by  
 221 Rwiza et al. (1992) [44].

## 222 **Objectives**

223 The main objective of this study is to identify the potential effect of long-term onchocerciasis  
 224 control measures using CDTi on the prevalence and incidence of epilepsy and NS in selected  
 225 villages in the Mahenge area of the Ulanga district in Tanzania. Based on the epidemiological  
 226 data available from 1989 by Rwiza et al., a comparison of prevalence and incidence from 2017 in  
 227 different age groups will allow testing for an association of epilepsy with onchocerciasis  
 228 interventions, specifically annual CDTi (Table 2).

230 **Table 2. The pre- and post-CDTi epilepsy study periods and estimated epilepsy prevalence**  
 231 **and incidence in the Mahenge area, Ulanga district in Tanzania.**

Mahenge area, Ulanga district, Tanzania		
Year of epilepsy study data collection	1989 [44]	2017
Status of CDTi at study year	Pre-CDTi	Post-CDTi (ongoing since 1997)
Estimated epilepsy prevalence	20.2/1000	14/1000*
Estimated epilepsy incidence	146/100'000	81.7/100'000**

232 \*Median epilepsy prevalence [4] and \*\*incidence in LMICs [3]

## 234 **Specific objectives**

235 1. To determine the prevalence of all forms of epilepsy in selected villages of the Mahenge area  
 236 and compare the related data from 2017 to the 1989 data.

- 1  
2  
3 237 2. To determine the incidence rate of annual new onset cases of all forms of epilepsy in the  
4  
5 238 Mahenge area and compare the related data from 2017 to the 1989 data.  
6  
7 239 3. To assess the ivermectin coverage and the onchocerciasis prevalence with a REMO  
8  
9 240 assessment in selected villages of the Mahenge area.  
10  
11 241 4. To determine the level of ongoing onchocerciasis transmission by a serological survey among  
12  
13 242 children in selected villages of the Mahenge area.  
14  
15 243 5. To investigate the potential difference in clinical appearance of epilepsy in patients with  
16  
17 244 negative onchocerciasis serology to patients with positive onchocerciasis serology.  
18

### 20 245 **Justification**

21  
22 246 The initial population based study from 1989 established the baseline prevalence of all forms of  
23  
24 247 epilepsy in the Ulanga district, Tanzania. With this 2017 population based study we aim to further  
25  
26 248 evaluate the prevalence and the incidence rate of new epilepsy cases, including a complete case  
27  
28 249 ascertainment of all forms of epilepsy encountered, and compare the data to the 1989 data. The  
29  
30 250 study includes an assessment of the ivermectin coverage in the study villages, and a concurrent  
31  
32 251 REMO assessment will provide the onchocerciasis prevalence estimate for 2017.  
33  
34  
35 252

## 36 253 **METHODS AND ANALYSIS**

### 37 254 **Study site and study population**

38  
39 255 The study will be carried out in the Mahenge area of the Ulanga district, Morogoro region in south-  
40  
41 256 eastern Tanzania, a mountainous area with fast flowing rivers. The population lives on  
42  
43 257 subsistence agriculture, livestock breeding, and also mining is practiced. Those villages that had  
44  
45 258 high epilepsy prevalence during the 1989 study will be selected for this presented study, namely  
46  
47 259 Mdindo, Vigoi and Misegezi [44].  
48  
49  
50 260

### 51 261 **Epilepsy and NS prevalence / incidence study**

#### 52 262 **Study design**

1  
2  
3 263 This study is designed as cross-sectional, population-based survey. A two-stage approach will be  
4  
5 264 applied for case identification within the villages. The gold-standard in neuro-epidemiological  
6  
7 265 surveys to identify epilepsy cases in LMICs is the door-to-door approach and this will be applied  
8  
9 266 [45]. All inhabitants of the selected villages will be eligible for participation and will be included in  
10  
11 267 the questionnaire screening survey. Due to well described limitations of questionnaire studies on  
12  
13 268 epilepsy (stigma leading to concealment of cases, recall bias, absence of clear terminology for  
14  
15 269 epilepsy and seizures) [3, 45], and to increase sensitivity of case ascertainment, key informants  
16  
17 270 who are likely to be aware of persons with epilepsy in the village will additionally be consulted  
18  
19 271 [45]. These may be health workers, traditional healers, teachers, community leaders or such [46].  
20  
21  
22 272 In a second stage, suspected cases of all forms of epilepsy identified during the household  
23  
24 273 screening survey will be further invited for clinical examination by a neurologist. The examination  
25  
26 274 will include neurological tests and a detailed interview for case verification. For all suspected  
27  
28 275 epilepsy cases their serological status will be determined using onchocerciasis rapid diagnostic  
29  
30 276 test (Ov16 RDT) (Standard diagnostics, Inc., Gyeonggi-do, Republic of Korea).

### 32 277 **Sample size calculation**

33  
34 278 According to Rwiza et al., 1992, the average prevalence of epilepsy in five villages with high  
35  
36 279 prevalence was 1.313% (Table 1). If we assume a reduction in the prevalence by 33.3% to be  
37  
38 280 able to compare the prevalence at a power of 80% and 95% confidence level, the minimal  
39  
40 281 sample size of 4,746 individuals will be required. Assuming a participation of 80%, a minimum  
41  
42 282 source population of 5,933 is necessary to obtain optimal sample size.  
43  
44 283 Since 1989 the population in the villages with high epilepsy prevalence has increased (Table 3).  
45  
46 284 For this survey we will include only the population or part of the population of the villages with the  
47  
48 285 highest epilepsy prevalence in 1989. The total population of the selected villages of Mdingo,  
49  
50 286 Vigoi and Misegezi is about 6'600.

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53  
54 287

288 **Table 3. List of the study villages in the Mahenge highlands, Tanzania, and their**  
 289 **population size in 1989 and in 2016.**

Name of Village (1989)	Population size (1989)	Population size (2016)
Mdindo	539	1536
Vigoi**	1822	2572
Misegezi	1667	3658*
Matumbala <sup>#</sup>	-----	1426
<b>Total</b>	<b>6977</b>	<b>9192</b>

\*Population projection based on the growth rate of Vigoi village; \*\*Vigoi has undergone a village separation and was split in two villages in 2010 (Vigoi and <sup>#</sup>Matumbala)

290

291 **Data collection at community level**

292 The community survey will commence by a questionnaire interview with the village authorities on  
 293 demographic topics, and with village health workerw to address general questions on the status  
 294 of epilepsy and epilepsy treatment in the village. Following, a complete door-to-door active  
 295 screening for suspected epilepsy cases at village level will be performed. The interviewer team  
 296 will be trained on how to conduct the active search for epilepsy cases using a pre-tested,  
 297 validated screening questionnaire targeting epilepsy by 5 specific questions [47, 48]. The  
 298 questionnaire will be translated in Kiswahili and will include the locally used terms for the two  
 299 respective conditions (epilepsy: *kifafa*, NS: *kusinzia kichwa*). To ascertain completeness and to  
 300 ensure the best collaboration with the village population, the interviewer team will be  
 301 accompagnied to all households by local village health workers in each individual village.  
 302 Together with the screening data, the geographical coordinates of the participating households  
 303 will be collected for the mapping and geospatial analysis of cases (proximity to rivers, potential  
 304 clustering).

### 305 **Case verification and validation**

306 All suspected epilepsy cases identified during the door-to-door survey will be verified by a  
 307 medical doctor/neurologist. The neurologist will perform a detailed anamnesis on all suspected

1  
2  
3 308 NS and epilepsy cases. In case of confirmation of the epilepsy and / or NS diagnosis, the  
4  
5 309 neurologist will perform a medical examination and administer a detailed questionnaire on the  
6  
7 310 type of epilepsy. Newly diagnosed epilepsy cases will be referred to an epilepsy treatment  
8  
9 311 centre. In case the person is already followed in a treatment centre, permission will be asked to  
10  
11 312 review the medical information available in the treatment centre to record epilepsy diagnosis and  
12  
13 313 epilepsy treatment history.

#### 15 314 **Definitions:**

- 17  
18 315 - A case of epilepsy will be defined according to the International League Against Epilepsy  
19  
20 316 (ILAE) guidelines as a patient who had (1) at least two times, unprovoked and without  
21  
22 317 fever, lost consciousness with convulsions with a minimal time difference of 24h between  
23  
24 318 the two events or (2) one unprovoked seizure and a probability of future seizures similar  
25  
26 319 to the general recurrence risk after 2 unprovoked seizures [49, 50].  
27  
28 320 - A case will be considered as active epilepsy if the patient is receiving epilepsy treatment  
29  
30 321 or, if without anti-epileptic treatment, the patient presented at least one seizure during the  
31  
32 322 last 5 years.  
33  
34 323 - A case of suspected NS will be defined as a person who presented with episodes of  
35  
36 324 decreased consciousness during which the head dropped forward repeatedly.  
37  
38 325 - New cases of epilepsy will be defined as cases that appeared within the last 12 month  
39  
40 326 proceeding the study period.  
41  
42  
43 327

#### 45 328 **Onchocerciasis prevalence study**

##### 47 329 **Study design**

49 330 This study includes two parts. I part one, the aim is to determine the onchocerciasis prevalence  
50  
51 331 in the selected villages after 20 years of CDTi by performing the WHO proposed REMO  
52  
53 332 methodology [51]. In brief, in each study village, 50 adults aged at least 20 years old and resident  
54  
55 333 in the community for at least 10 years, will be invited to participate. They will be examined for the



334 presence of onchocerciasis nodules (subcutaneous nodules or deep, painless, firm, mobile  
 335 nodules over bony prominences: pelvic girdle, costal grid, knees, and skull).  
 336 The second part aims at determining the level of ongoing transmission of onchocerciasis in the  
 337 selected villages. Therefore, serological testing for onchocerciasis will be done in all children at  
 338 ages 7-10 years old, using the onchocerciasis specific Ov16 RDT (Standard diagnostics, Inc.,  
 339 Gyeonggi-do, Republic of Korea). According to the National Census survey in 2012, the  
 340 population of children aged 7-10 years represented 11.6% of the population in Ulanga district.  
 341 Estimated population of children aged 7-10 years from the four selected villages is 1065 of which  
 342 746 (~70%) are anticipated to participate in the survey giving a power of 85% in detecting the  
 343 prevalence between 0.8 to 2% at 5% significance level (Table 4).

344

345 **Table 4. Estimated number of children aged 7 to 10 years old in the study villages in the**  
 346 **Ulanga district, Tanzania, in 2016.**

Name of Village	Population size (1989)	Population size (2016)	Estimated Population aged 7-10 yrs	Estimated 80% of children (7-10 yrs)
Mdindo	539	1536	178	143
Vigoi**	1822	2572	298	239
Misegezi	1667	3658*	424*	339*
Matumbala <sup>#</sup>	-----	1426	165	132
<b>Total</b>	<b>7007</b>	<b>9192</b>	<b>1065</b>	<b>745</b>

\*Population projection based on the growth rate of Vigoi village \*\*Vigoi has undergone a village separation and was split in two villages in 2010 (Vigoi and <sup>#</sup>Matumbala)

347

#### 348 **Data collection procedures**

349 Data collection will be done using tablet computers. All data collection forms are developed in the  
 350 open source software 'Open Data Kit' (ODK, <https://opendatakit.org/>). Interviewers will be trained  
 351 in how to perform tablet computer based surveys. A technical data coordinator is assigned to

1  
2  
3 352 guarantee completeness and quality of data, and to assure daily data transfer from each tablet  
4  
5 353 computer to the central server for data security.

#### 7 354 **Data management and analysis**

9 355 The prevalence of epilepsy and NS will be computed as a ratio of the number of epilepsy and NS  
10  
11 356 cases per total number of people registered in the households visited. The epidemiological  
12  
13 357 distribution of families with and without epilepsy will be compared. The ratio of new epilepsy and  
14  
15 358 NS cases per number of people registered in the household will be compared between villages  
16  
17 359 and correlated with onchocerciasis prevalence data. Demographic and clinical characteristics of  
18  
19 360 persons with epilepsy having a positive Ov16 serology will be compared to epilepsy cases with  
20  
21 361 negative Ov16 serology.

#### 24 362 **Data storage and handling**

26 363 All data files will be centralised and stored in a secure central server. Name-linked information on  
27  
28 364 participants and ID codes will remain confidential and will be used only to communicate clinical  
29  
30 365 results to participants for their respective treatments.

#### 32 366 **Ethical considerations**

34 367 The study will be carried out adhering to the principles of the Declaration of Helsinki; to all other  
35  
36 368 applicable regulations, and according to established international scientific standards.

38 369 After having obtained ethics approval from the responsible ethics committees in Belgium and  
39  
40 370 Tanzania, before the activities start, the research team will hold meetings with village and  
41  
42 371 community leaders and health workers of the selected villages. The procedure, purpose and  
43  
44 372 specific aim of the present study will be explained and discussed in regard to the potential risks  
45  
46 373 and benefits for the community. Community leaders, village health workers and researcher will  
47  
48 374 maintain the initially established communication for the entire duration of the study. The  
49  
50 375 dissemination of results will be organized in a similar way as the initial meeting.

53 376 As approved by the relevant ethics committees, only participants who provide written informed  
54  
55 377 consent will be enrolled in the study. Participant information sheets and consent forms will be

1  
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3 378 available in English and Kiswahili. In case of illiteracy, information sheets and consent forms will  
4  
5 379 be read to the participant in the presence of a witness. All participants are permitted to withdraw  
6  
7 380 from the study activities, without reason, at any time. All personal information, samples and test  
8  
9 381 results will be encoded and treated confidentially. Spatial information will be presented in a way  
10  
11 382 that no individual data can be extrapolated. People identified with untreated epilepsy or with  
12  
13 383 interrupted treatment will be referred to the treatment centre and receive advice for care and  
14  
15 384 support.  
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18 385

## 19 386 **DISCUSSION**

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21  
22 387 The central research question of this study is to determine whether mass drug administration of  
23  
24 388 ivermectin using the CDTi methodology has the potential to prevent the onset of onchocerciasis  
25  
26 389 associated epilepsy. The expected results will contribute to a better understanding of the linkage  
27  
28 390 between the onset of epilepsy and NS in particular, onchocerciasis and the impact of CDTi. In  
29  
30 391 northern Uganda, an NS epidemic stopped after introducing a programme combining CDTi and  
31  
32 392 larviciding of the main rivers. This study will be the first to investigate systematically whether  
33  
34 393 CDTi alone may reduce epilepsy in an onchocerciasis endemic region.  
35

36  
37 394 With the Ov16 serological survey among children between the age 7-10 we will be able to  
38  
39 395 estimate the ongoing transmission of onchocerciasis in the Mahenge area after 20 years of CDTi.  
40

41 396 So far, the onchocerciasis control program in the study area was monitored based on annual  
42  
43 397 ivermectin coverage data provided by the community directed distributors of ivermectin. With this  
44  
45 398 study we will obtain ivermectin coverage data by interviewing the population. Moreover, by  
46  
47 399 performing an Ov16 seroprevalence study among children under the age of 10 years we will  
48  
49 400 obtain a real-time estimate of the level of ongoing transmission of onchocerciasis. Hopefully,  
50  
51 401 results will show a low Ov16 seroprevalence in children and a decreased prevalence of epilepsy  
52  
53 402 since 1989. In case a high Ov16 seroprevalence is found this will suggest that the CDTi  
54  
55 403 programme was performing suboptimal and/or that ivermectin resistance may have developed.  
56  
57

1  
2  
3 404 In pre- and post-CDTi comparison it is possible that observed differences in epilepsy prevalence  
4  
5 405 and incidence are not related to the intervention (CDTi) but to some of the other factors (e.g.  
6  
7 406 those mentioned in Fig. 1) that might have changed over time. However, a site visit to the  
8  
9 407 Mahenge study site revealed that the village population had increased by a factor of 3, but there  
10  
11 408 was no important in- or out migration or any other major change in lifestyle of the population or  
12  
13 409 another major environmental change. In all the villages included in the study, such potential  
14  
15 410 changes will be carefully assessed to control for potential confounding factors. Families who  
16  
17 411 migrated into the study area after the implementation of CDTi will not be included in the analyses.  
18  
19

## 20 412 **Outlook**

21  
22 413 This study aims to unveil the potential effect of CDTi on reducing the incidence of epilepsy in  
23  
24 414 onchocerciasis endemic areas. The results will provide an evidence base for to strengthen CDTi  
25  
26 415 programs for the elimination goal for onchocerciasis and that has the power to prevent new  
27  
28 416 cases of epilepsy associated to onchocerciasis. The results and lessons learned from this study  
29  
30 417 will be published in open access journals, as well as presented at conferences and shared with  
31  
32 418 all interested health authorities in Tanzania and beyond.  
33  
34

35 419

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37  
38  
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40  
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42  
43 423 information and practical considerations for the development of the current study protocol.  
44  
45

46 424

## 47 425 **Authors' contribution**

48  
49 426 All listed authors contributed to the development of the study design, essential study documents  
50  
51 427 and study tools. According to their different areas of expertise, the authors critically revised  
52  
53 428 specific parts of this manuscript: HG wrote the manuscript; HG, BM, PS, RC developed the study  
54  
55 429 protocol; WM, MM, WM developed and approved the neurological study protocol and the survey  
56  
57

1  
2  
3 430 tools; HG, BM, AK, developed the methodology and tools for the digital data collection; HG, BM,  
4  
5 431 RC visited the study sites.  
6

7 432

8  
9 433 **Competing interests**

10  
11 434 The authors declare that they have no competing interests.  
12

13 435

14  
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18  
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20  
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22  
23

24 440

25  
26 441 **Ethics approval**

27  
28 442 The protocol has received ethical approval from the ethics committee of the University of  
29  
30 443 Antwerp, Antwerp, Belgium (29.08.2016) and the National Institut of Medical Research (NIMR)  
31  
32 444 ethical committee Dar es Salaam, Tanzania (24.08.2016).  
33

34 445

35  
36 446 **Data sharing statement**

37  
38 447 The data for this study will be collected in 2017 and published in peer-reviewed open access  
39  
40 448 journals. Additionally, data will be extracted from a published article (Rwiza et al., 1992) as  
41  
42 449 described in details the methods section.  
43  
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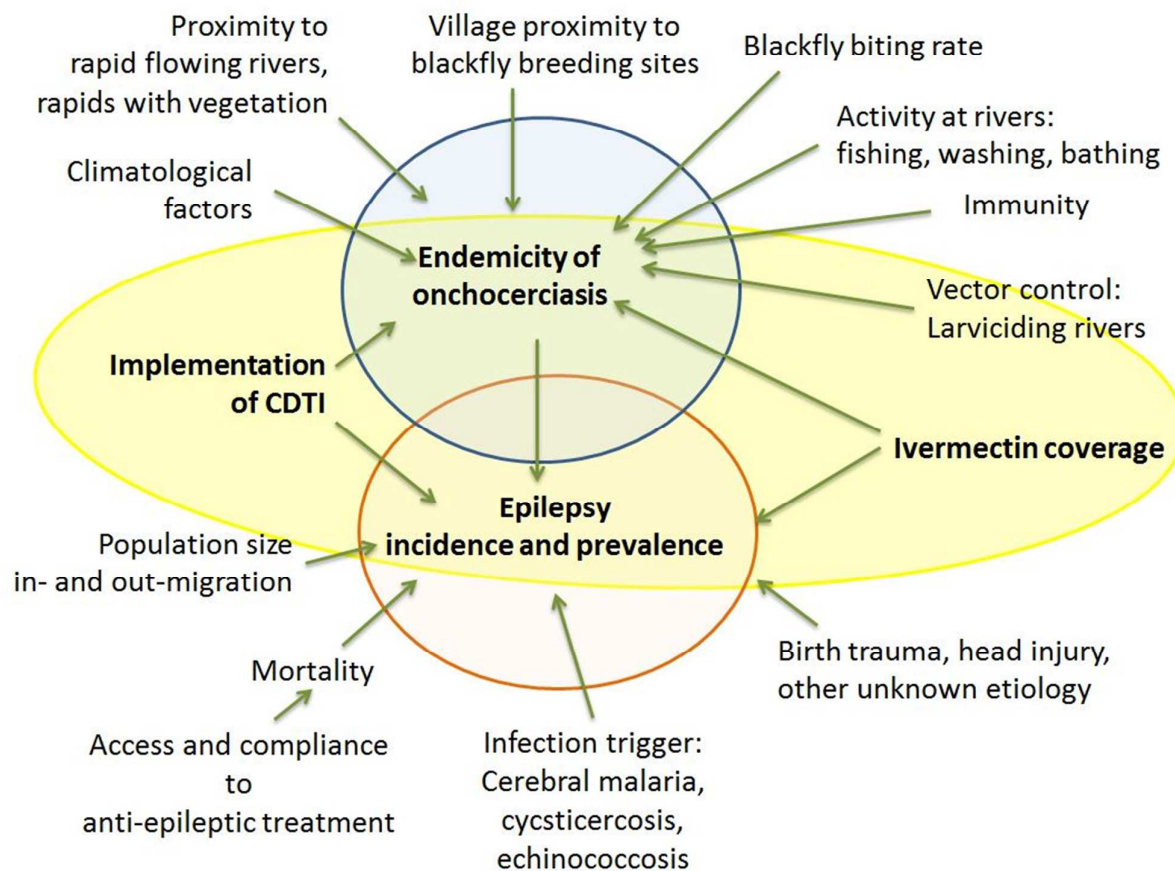
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**Figure 1. There is an extensive network of controllable and uncontrollable factors influencing the level of onchocerciasis endemicity and prevalence and incidence of associated epilepsy. This project investigates the effect of community directed treatment with ivermectin on the endemicity of onchocerciasis and the incidence and prevalence of epilepsy.**

# BMJ Open

## Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for onchocerciasis, and the potential impact of community-directed treatment with ivermectin: a cross sectional study and comparison over 28 years

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3 1 **Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for**  
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5 2 **onchocerciasis, and the potential impact of community-directed treatment with**  
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7 3 **ivermectin: a cross sectional study and comparison over 28 years**  
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## 17 **ABSTRACT**

### 18 **Introduction**

19 Worldwide, there are an estimated 50 million people affected by epilepsy. Its etiology is manifold,  
20 and parasitic infections play an important role, specifically onchocerciasis. From onchocerciasis  
21 endemic areas a distinctive form of epilepsy has been described as nodding syndrome, affecting  
22 children and causing nodding seizures, mental retardation and debilitating physical development.  
23 Onchocerciasis is treatable with ivermectin. Control programs using community directed  
24 treatment with ivermectin (CDTI) are implemented in endemic countries. This study is designed  
25 to contribute to a better understanding of the linkage between the onset of epilepsy,  
26 onchocerciasis and CDTI. Comparing the epidemiological data on epilepsy and onchocerciasis  
27 from pre-CDTI and 20 years after its introduction will allow identifying a potential impact of  
28 ivermectin on the onset of epilepsy.

### 29 **Methods and analysis**

30 The study will be conducted in the Mahenge highlands in Tanzania. Study site selection is based  
31 on an in-depth study on epilepsy in that area dating from 1989. CDTI was introduced in 1997. By  
32 a door-to-door approach, the population will be screened for epilepsy using a validated  
33 questionnaire. Suspected cases will be invited for a neurological examination for case  
34 verification. Onchocerciasis prevalence will be assessed by a rapid epidemiological assessment  
35 for prevalence. As an indicator for ongoing transmission, children younger than 10 years of age  
36 will be tested for Ov16 antibodies. Ivermectin use will be assessed at household level. Epilepsy  
37 data will be analysed in comparison to the 1989 data to reveal pre- and post-CDTI  
38 implementation prevalence and incidence.

### 39 **Ethics and dissemination**

40 The protocol has received ethical approval from the ethics committees of the University of  
41 Antwerp, Belgium and of the National Institut of Medical Research (NIMR), Dar es Salaam,

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2  
3 42 Tanzania. The findings will be published in peer-reviewed journals, and presented to the health  
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5 43 authorities in Tanzania, at national, regional and village level.  
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8  
9 45 **Strengths and limitations of this study:**

- 10  
11 46 • This study will allow comparison of large scale population based data on epilepsy  
12  
13 epidemiology in Mahenge over 28 years.  
14  
15 47  
16 48 • This comparison will answer key questions on the potential impact of community directed  
17  
18 49 treatment with ivermectin (CDTI) targeting onchocerciasis on epilepsy prevalence and  
19  
20 50 incidence.  
21  
22 51 • The pre-CDTI epilepsy survey in Tanzania dates from 1989 and adjusting for potential  
23  
24 52 confounding factors other than CDTI that may influence epilepsy incidence and prevalence  
25  
26 53 in the area need to be carefully assessed.  
27  
28 54 • Minor differences in the study methodology used in 1989 and 2017 will limit the data  
29  
30 55 comparison to prevalence and incidence at village level.  
31  
32 56 • Focusing on villages with high epilepsy burden in the past may lead to an overestimation of  
33  
34 57 the potential impact of CDTI.  
35  
36  
37 58

38  
39 59 **Key words**

40  
41 60 Epilepsy  
42  
43 61 Nodding disease  
44  
45 62 Onchocerciasis  
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47 63 Ivermectin  
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49 64 Tanzania  
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54 66 **INTRODUCTION**

55  
56 67 **Epilepsy in onchocerciasis endemic regions in Africa**  
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2  
3 68 Epilepsy is a chronic disease estimated to affect 50 million people worldwide according to World  
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5 69 Health Organisation (WHO).<sup>1</sup> In general, higher prevalence and incidence are reported from  
6  
7 70 those populations living in low and middle income countries (LMICs) when compared to  
8  
9 71 industrialized countries.<sup>2 3</sup> In fact, more than 85% of the global burden of epilepsy occurs in the  
10  
11 72 people living in LMICs.<sup>4 5</sup> The etiology of epilepsy is very diverse and not yet fully understood.  
12  
13 73 Besides birth trauma and head injury involving the brain, infectious diseases can trigger epilepsy  
14  
15 74 as well. Several parasitic infections are associated with epilepsy such as cerebral malaria,  
16  
17 75 neurocysticercosis, echinococcosis, and onchocerciasis.<sup>6-8</sup> Many of these epilepsy cases could  
18  
19 76 be prevented through timely anti-parasitic treatment. Epilepsy manifests in a variety of seizure  
20  
21 77 types and degrees of intensity.<sup>9</sup> In Tanzania, Uganda and South Sudan, a distinct form of  
22  
23 78 epilepsy has been described as nodding syndrome (NS).<sup>10-12</sup> NS is a debilitating epileptic  
24  
25 79 disorder mainly affecting children at the ages of 3 and 18 years.<sup>13</sup> The seizures are characterized  
26  
27 80 by a brief loss of muscle-tone in the neck, leading to repetitive head-nodding.<sup>14</sup> NS is often  
28  
29 81 associated with cognitive decline, and sometimes with stunted growth.<sup>15</sup> So far, NS is solely  
30  
31 82 described in onchocerciasis endemic areas.<sup>10</sup> Since its first description from Tanzania in the  
32  
33 83 1960s until the until the mid-1990s NS was a rare condition in African countries.<sup>16 17</sup> A NS  
34  
35 84 epidemic has been observed in the past two decades in northern Uganda and in neighboring  
36  
37 85 South Sudan.<sup>18 15</sup> The weight of the public health burden caused by NS can be illustrated by the  
38  
39 86 situation in the West Equatorial State in South Sudan, where in the village of Mvolo, over 50% of  
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41 87 the families had at least one child affected by epilepsy of the NS type, resulting in one in six  
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43 88 children of the village suffering from epilepsy.<sup>19</sup>  
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46  
47 89 Health systems services in remote rural regions in Africa are rarely capable to provide continuous  
48  
49 90 anti-epileptic treatment to those patients in need.<sup>5</sup> Further more, most health care workers lack  
50  
51 91 training to diagnose and treat persons with epilepsy adequately. In many societies in Africa, and  
52  
53 92 in addition to the clinical burden, epilepsy is perceived as a possession by evil spirits and hence  
54  
55 93 bears a stigma that puts the diseased individual and his family at risk for social isolation.<sup>20</sup>

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3 94 Moreover, the family's economy is negatively impacted by the disease, since an epileptic family  
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5 95 member needs specific care and supervision, detaining care takers from their subsistence  
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7 96 duties.<sup>21</sup>  
8

9  
10 97 NS only occurs in onchocerciasis endemic areas. An epidemiological association between  
11  
12 98 epilepsy and onchocerciasis was first reported from western Uganda in the early 1990ties.<sup>22 23</sup> A  
13  
14 99 case-control study performed in 1991-92 in the Mbam valley in Cameroon demonstrated a  
15  
16 100 significantly higher microfilarial load in persons with epilepsy than in controls.<sup>24</sup> Study results from  
17  
18 101 other onchocerciasis-endemic African countries underline this association.<sup>8 25</sup> Case-control  
19  
20 102 studies in northern Uganda and South Sudan focusing on NS patients produced similar results,  
21  
22 103 showing a higher prevalence of onchocerciasis in NS cases compared to non-epileptic controls.<sup>15</sup>  
23  
24 104 <sup>18</sup> It is, however, unclear how onchocerciasis might cause NS. Although the eye and the optical  
25  
26 105 nerve are affected when onchocerciasis causes blindness, microfilariae and adult *Onchocerca*  
27  
28 106 *volvulus* worms are not generally considered to be able to invade the central nervous system.  
29  
30 107 Recent research hypothesises that an immunological cross-reaction of onchocerciasis-specific  
31  
32 108 antibodies may provoke a neurotoxic reaction and trigger NS.<sup>26</sup>  
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### 37 110 **Onchocerciasis, a treatable neglected tropical disease facing obstacles on the road to** 38 39 111 **elimination**

40  
41 112 Onchocerciasis is a parasitic disease caused by an infection with the the worm *O. volvulus*  
42  
43 113 whose filarial larvae are transmitted by blackflies (*Simuliidae* spp.). In the final host, humans, the  
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45 114 adult female worms encapsulate in the subcutaneous tissue forming visually detectable nodules.  
46  
47 115 Each female worm releases up to one thousand microfilariae per day. These microfilariae  
48  
49 116 provoke itching, dermatitis and – if left untreated – blindness, which led to the disease also being  
50  
51 117 called river blindness. Blackflies get infected with microfilariae when biting infected humans in  
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53 118 proximity to fast flowing rivers, the breeding site of the blackflies. After passing through several  
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55 119 larval stages, infected blackflies spread the parasite by biting other people. Onchocerciasis is

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3 120 treatable with ivermectin.<sup>27</sup> The drug has a twofold mechanism of action: (i) it kills the  
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5 121 microfilariae and (ii) it inhibits their release by the adult female worm for up to two years after a  
6  
7 122 single dose treatment.<sup>28</sup> Hence, ivermectin has a strong impact on reducing transmission.  
8  
9 123 However, ivermectin is not lethal to adult worms and infected persons have to take it annually for  
10  
11 124 up to 15 years.<sup>29</sup> Onchocerciasis is a priority disease scheduled for elimination by 2025 by the  
12  
13 125 WHO. Today, 99% of the globally 37 million people infested live in Africa.<sup>1</sup> In 1995, the African  
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15 126 Program for Onchocerciasis Control (APOC) was initiated for the implementation of the  
16  
17 127 onchocerciasis control programme based on community directed treatment with ivermectin  
18  
19 128 (CDTI). APOC was coordinating these activities in endemic areas of 22 African countries.<sup>30</sup> Since  
20  
21 129 May 2016, CDTI control programmes are integrated in the WHO Expanded Special Project for  
22  
23 130 Elimination of Neglected Tropical Diseases (ESPEN).<sup>31</sup> CDTI overcomes the limited performance  
24  
25 131 of weak health systems in rural areas by using an active, strategic involvement of the  
26  
27 132 community.<sup>32</sup> To reach the entire population, ivermectin distribution is organized by trained  
28  
29 133 volunteers in each village, resulting in a large geographical coverage. CDTI, in certain regions  
30  
31 134 combined with the control of the blackfly by larviciding of breeding sites (i.e. fast flowing rivers),  
32  
33 135 resulted in a measurable impact reflected by a remarkable transmission reduction in the past 20  
34  
35 136 years.<sup>33</sup> But success and effectiveness of these targeted interventions lack comprehensiveness.  
36  
37 137 Certain onchocerciasis endemic regions remain undersupplied or unreachable for CDTI due to  
38  
39 138 political instability, insecurity or armed conflicts.<sup>34</sup> As a consequence in the war-affected regions  
40  
41 139 of South Sudan and northern Uganda, onchocerciasis control measures were stopped or  
42  
43 140 implementation started only recently. Moreover, misconceptions and the fear of adverse effects  
44  
45 141 result in suboptimal therapeutic coverage and reduce the effectiveness of the control program.<sup>35</sup>  
46  
47 142 Adding to the complexity of onchocerciasis control, in regions where *Loa loa* and onchocerciasis  
48  
49 143 are co-endemic, ivermectin may cause severe adverse effects (encephalopathy, coma or death)  
50  
51 144 in *Loa loa* infected individuals with high microfilariae load.<sup>36 37</sup> Thus, CDTI implementation in such  
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53 145 regions requires additional precautions.<sup>38</sup> This is the case in certain regions of Cameroon and the  
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3 146 DRC.<sup>39</sup> Compliance to CDTI programs can also decrease over the years since less direct positive  
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5 147 effects can be observed when onchocerciasis prevalence drops, and healthy feeling people may  
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7 148 not appreciate the importance of continuing repeated treatment.<sup>40</sup>  
8

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11 150 **The potential of CDTI to reduce the incidence of epilepsy in onchocerciasis endemic**  
12  
13 **regions**  
14 151

15 152 The endemicity of onchocerciasis and the prevalence and incidence of epilepsy are influenced by  
16  
17 153 a multitude of factors (Figure 1). These factors are of uncontrollable nature (climate,  
18  
19 154 environment, ecology), and of controllable nature (prevention and intervention programs, access  
20  
21 155 to health care and treatment). The controllable factors can be addressed. I.e. onchocerciasis  
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23 156 cases can be cured and hence new onchocerciasis associated epilepsy (OAE) cases can be  
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25 157 prevented.  
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30 159 <<<<<<Figure 1 near here>>>>>>>>  
31

32 160  
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34 161 The two heavily affected regions of the last decades, Northern Uganda and South Sudan, were –  
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36 162 and South Sudan still is - affected by armed conflicts. In 2012, after the conflict ended in northern  
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38 163 Uganda, the NS epidemic was investigated. Following on, epilepsy treatment was provided,  
39  
40 164 biannual CDTI was implemented and larviciding of major rivers was carried out.<sup>41</sup> Since 2013 the  
41  
42 165 NS epidemic in northern Uganda has reportedly been halted.<sup>42</sup> In contrast in South Sudan, where  
43  
44 166 CDTI was stopped because of insecurity, new cases of NS continue to appear.<sup>19</sup> Based on the  
45  
46 167 observations from northern Uganda, it has been suggested that ivermectin may reduce the  
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48 168 incidence of NS and other forms of epilepsy in onchocerciasis endemic areas.<sup>43</sup> Considering that  
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50 169 30% of the globally 37 million individuals infected with onchocerciasis do not have access to  
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52 170 effective treatment, and that 1% of those develop epilepsy (equivalent to the estimated excess  
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171 prevalence of epilepsy over non-onchocerciasis areas) the number of excess cases of epilepsy  
 172 attributed to onchocerciasis could exceed 100'000.<sup>1 7</sup>

173 Recent observations in the DRC and northern Uganda suggest that optimal treatment coverage  
 174 of ivermectin may stop the incidence of NS and other forms of OAE.<sup>43</sup>

175

## 176 **Aim**

177 The population based study from 1989 by Rwiza et al. established the baseline prevalence of all  
 178 forms of epilepsy in the Ulanga district, Tanzania.<sup>44</sup> With this 2017 population based study we  
 179 aim to further evaluate the prevalence and the incidence rate of new epilepsy cases, including a  
 180 complete case ascertainment of all forms of epilepsy encountered, and compare the data to the  
 181 1989 data (Table 1).

182

183 **Table 1. The pre- and post-CDTI epilepsy study periods and estimated epilepsy prevalence**  
 184 **and incidence in the Mahenge area, Ulanga district in Tanzania.**

Mahenge area, Ulanga district, Tanzania		
Year of epilepsy study data collection	1989 <sup>44</sup>	2017
Status of CDTI at study year	Pre-CDTI	Post-CDTI (ongoing since 1997)
Estimated epilepsy prevalence	20.2/1000	14/1000*
Estimated epilepsy incidence	146/100'000	81.7/100'000**

185 \*Median epilepsy prevalence and \*\*incidence in low and middle income countries<sup>4 3</sup>

186

## 187 **Objective**

188 The main objective of this study is to identify the potential impact of long-term onchocerciasis  
 189 control measures using CDTI on the prevalence and incidence of epilepsy in selected villages in  
 190 the Mahenge area of the Ulanga district in Tanzania.

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5 192 **Specific objectives**  
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7 193 1. To determine the prevalence of all forms of epilepsy in selected villages of the Mahenge area  
8  
9 194 and compare the related data from 2017 to the 1989 data.  
10  
11 195 2. To determine the incidence rate of annual new onset cases of all forms of epilepsy in the  
12  
13 196 Mahenge area and compare the related data from 2017 to the 1989 data.  
14  
15 197 3. To assess the ivermectin coverage and the onchocerciasis prevalence with a REMO  
16  
17 198 assessment in selected villages of the Mahenge area.  
18  
19 199 4. To determine the level of onchocerciasis transmission by a serological survey using a rapid  
20  
21 200 test among children in selected villages of the Mahenge area.  
22  
23 201 5. To investigate the potential difference in clinical appearance of epilepsy in patients with  
24  
25 202 negative onchocerciasis serology to patients with positive onchocerciasis serology.  
26  
27  
28 203

## 204 **METHODS AND ANALYSIS**

205 The study consists of two parts: (I) a study to determine the prevalence and incidence of epilepsy  
206 and (II) a study to determine ivermectin coverage, onchocerciasis prevalence and level of  
207 transmission. Data collection is carried out between January and September 2017. Analysis is  
208 planned to be finalized by end of 2017, to allow publishing of the results in 2018.

### 209 **Study site**

210 The study will be carried out in the Mahenge area of the Ulanga district, Morogoro region in south-  
211 eastern Tanzania, a mountainous area with fast flowing rivers.

### 212 **Epilepsy in the Mahenge area**

213 In the 1960s, Aall-Jilnek was the first to report a high burden of epilepsy in the Mahenge area,  
214 and also described the first NS cases.<sup>16</sup> In 1989, Rwiza et al. carried out a population based  
215 survey to determine prevalence and incidence of epilepsy in the Ulanga district and found an  
216 annual incidence of 73.3 new cases in 100 000. The prevalence was 10.2 cases in 1000, and

217 varied between villages from 5.1 to 37.1 cases in 1000. Those villages with the highest  
 218 prevalence were located in the Mahenge highlands (Table 2).<sup>44</sup>

219  
 220 **Table 2. Population size and prevalence of epilepsy in those villages of the Ulanga district,**  
 221 **Tanzania, showing the highest prevalence in 1989, as reported by Rwiza et al. in 1992**

Name of Village	Population size	Number of Epilepsy cases	Prevalence per 1000 people
Sali <sup>δ</sup>	1282	14	10.9
Mdindo <sup>δ</sup>	539	20	37.1
Vigoi <sup>δ</sup>	1822	23	12.6
Lupiro	1697	17	10
Misegezi	1667	18	10.8
<b>Total</b>	<b>7007</b>	<b>92</b>	<b>13.13</b>

222 <sup>δ</sup>Located in Mahenge highlands

### 224 **Onchocerciasis and CDTI in the Mahenge area**

225 The Morogoro region is among the five regions where onchocerciasis is endemic. The region  
 226 presents four foci: Uluguru mountain, Ulanga/Mahenge, Kilosa and the Nguru mountain focus.<sup>45</sup>

227 The Ulanga district, specifically the Mahenge area, was known for its high endemicity of  
 228 onchocerciasis since the early last century.<sup>46</sup> Mass drug administration using annual CDTI was

229 introduced in the Mahenge area in 1997.<sup>47</sup> Before CDTI was implemented, 58.6% of a sample of  
 230 482 inhabitants of the Mahenge area were found to have a microfilariae positive skin snip.<sup>48</sup>

231 Twelve years later, in 2009 during the rapid epidemiological mapping of onchocerciasis (REMO)  
 232 in 10 villages in the Mahenge area, the percentage of persons with a microfilariae positive skin  
 233 snip has dropped to 21.9%, with a mean village prevalence of 8.3%.<sup>33</sup>

### 234 **Study population**

1  
2  
3 235 Those villages that had high epilepsy prevalence during the 1989 study will be selected for this  
4  
5 236 study, namely Mdingo, Vigoi and Mizegezi.<sup>44</sup> Of these villages, the entire population will be  
6  
7 237 included in the study.  
8

9 238

## 11 239 **Epilepsy and NS prevalence / incidence study**

### 13 240 **Study design**

15 241 The study is designed as cross-sectional, population-based study, following atwo-stage approach  
16 242 for epilepsy case identification at village level. The gold-standard in neuro-epidemiological  
17 243 surveys to identify epilepsy cases in LMICs is the door-to-door approach and this will be  
18 244 applied.<sup>49</sup> All inhabitants of the selected villages will be eligible for participation and will be  
19 245 included in the questionnaire screening survey. Due to well described limitations of questionnaire  
20 246 studies on epilepsy (stigma leading to concealment of cases, recall bias, absence of clear  
21 247 terminology for epilepsy and seizures) and to increase sensitivity of case ascertainment, key  
22 248 informants who are likely to be aware of persons with epilepsy in the village will additionally be  
23 249 consulted.<sup>3 49</sup> These may be health workers, traditional healers, teachers, or community  
24 250 leaders.<sup>50</sup>

26 251 In a second stage, suspected cases of all forms of epilepsy identified during the household  
27 252 screening survey will be further invited for clinical examination by a neurologist. The examination  
28 253 will include neurological tests and a detailed interview for case verification. In verified epilepsy  
29 254 cases the onset of the seizures will be determined and possible etiologic factors will be  
30 255 investigated, such as birth trauma, head injury, meningo-encephalitis, cerebral malaria,  
31 256 neurocystocercosis, and the history of onchocerciasis. For all suspected epilepsy cases their  
32 257 serological status will be determined using onchocerciasis rapid diagnostic test (Ov16 RDT)  
33 258 (Standard diagnostics, Inc., Gyeonggi-do, Republic of Korea).

### 35 259 **Sample size calculation**



260 According to Rwiza et al., 1992, the average prevalence of epilepsy in five villages with high  
 261 prevalence was 1.313% (Table 2). If we assume a reduction in the prevalence by 33.3% to be  
 262 able to compare the prevalence at a power of 80% and 95% confidence level, the minimal  
 263 sample size of 4,746 individuals will be required. Assuming a participation of 80%, a minimum  
 264 source population of 5,933 is necessary to obtain optimal sample size.  
 265 Since 1989 the population in the villages with high epilepsy prevalence has increased (Table 3).  
 266 For this survey we will include only the population of the villages with the highest epilepsy  
 267 prevalence in 1989. The total population of the selected villages of Mdindo, Vigoi and Misegezi in  
 268 2016 is about 7,766.

270 **Table 3. List of the study villages in the Mahenge highlands, Tanzania, and their**  
 271 **population size in 1989 and in 2016.**

Name of Village (1989)	Population size (1989)	Population size (2016)
Mdindo	539	1536
Vigoi**	1822	2572
Misegezi	1667	3658*
<b>Total</b>	<b>4028</b>	<b>7766</b>

\*Population projection based on the growth rate of Vigoi village;

272  
 273 **Data collection at community level**  
 274 The community survey will commence by a questionnaire interview with the village authorities on  
 275 demographic topics, and with village health workers to address general questions on the status  
 276 of epilepsy and epilepsy treatment in the village. Following, a complete door-to-door active  
 277 screening for suspected epilepsy cases at village level will be performed. The interview team will  
 278 be trained on how to conduct the active search for epilepsy cases using a pre-tested, validated  
 279 screening questionnaire targeting epilepsy by 5 specific questions (provided in the  
 280 supplementary material).<sup>51 52</sup> The questionnaire will be translated in Kiswahili and will include the

1  
2  
3 281 locally used terms for the two respective conditions (epilepsy: *kifafa*, NS: *kusinzia kichwa*). To  
4  
5 282 ascertain completeness and to ensure the best collaboration with the village population, the  
6  
7 283 interviewer team will be accompanied to all households by local village health workers in each  
8  
9 284 individual village. Together with the screening data, the geographical coordinates of the  
10  
11 285 participating households will be collected for the mapping and geospatial analysis of cases  
12  
13 286 (proximity to rivers, potential clustering).

### 15 287 **Case verification and validation**

16  
17  
18 288 All suspected epilepsy cases identified during the door-to-door survey will be verified by a  
19  
20 289 neurologist. The neurologist will perform a detailed anamnesis on all suspected NS and epilepsy  
21  
22 290 cases. In case of confirmation of the epilepsy and / or NS diagnosis, the neurologist will perform  
23  
24 291 a medical examination and administer a detailed questionnaire on the type of epilepsy. Newly  
25  
26 292 diagnosed epilepsy cases will be referred to an epilepsy treatment centre. In case the person is  
27  
28 293 already followed in a treatment centre, permission will be asked to review the medical information  
29  
30 294 available in the treatment centre to record epilepsy diagnosis and epilepsy treatment history.

### 32 295 **Definitions:**

- 33  
34  
35 296 - A case of epilepsy will be defined according to the International League Against Epilepsy  
36  
37 297 (ILAE) guidelines as a patient who had (1) at least two times, unprovoked and without  
38  
39 298 fever, lost consciousness with convulsions with a minimal time difference of 24h between  
40  
41 299 the two events or (2) one unprovoked seizure and a probability of future seizures similar  
42  
43 300 to the general recurrence risk after 2 unprovoked seizures.<sup>53 54</sup>  
44  
45 301 - A case will be considered as active epilepsy if the patient is receiving epilepsy treatment  
46  
47 302 or, if without anti-epileptic treatment, the patient presented at least one seizure during the  
48  
49 303 last 5 years.  
50  
51 304 - A case of suspected NS will be defined as a person who presented with episodes of  
52  
53 305 decreased consciousness during which the head dropped forward repeatedly.  
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3 306 - New cases of epilepsy will be defined as cases that appeared within the last 12 month  
4  
5 307 proceeding the study period.  
6

7 308 For comparison, the ILAE epilepsy case definition valid in 1989 will be applied, which means that  
8  
9 309 only cases with more than one seizure will be included in the comparison data analysis. Results  
10  
11 310 obtained by applying the current ILAE definition will be presented separately.  
12  
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## 15 312 **Onchocerciasis prevalence study**

### 16 313 **Study design**

17  
18 314 This study includes two approaches. In one approach, the aim is to determine the onchocerciasis  
19  
20 315 prevalence in the selected villages after 20 years of CDTI by performing the WHO proposed  
21  
22 316 REMO methodology.<sup>55</sup> In brief, in each study village, 50 adults aged at least 20 years old and  
23  
24 317 resident in the community for at least 10 years, will be invited to participate. They will be  
25  
26 318 examined for the presence of onchocerciasis nodules (subcutaneous nodules or deep, painless,  
27  
28 319 firm, mobile nodules over bony prominences: pelvic girdle, costal grid, knees, and skull).  
29  
30 320 Although pre-control onchocerciasis prevalence data from Mahenge is not available at village  
31  
32 321 level, onchocerciasis transmission in the study villages is shown by an entomological study  
33  
34 322 carried out in the 1960ties and found a high number of the blackflies contained infective L3 stage  
35  
36 323 parasites in their heads.<sup>56</sup>  
37  
38

39 324 The second part aims at determining the level of transmission of onchocerciasis in the selected  
40  
41 325 villages. Therefore, serological testing for onchocerciasis will be done in all children at ages 7-10  
42  
43 326 years old, using the onchocerciasis specific Ov16 RDT (Standard diagnostics, Inc., Gyeonggi-do,  
44  
45 327 Republic of Korea). According to the National Census survey in 2012, the population of children  
46  
47 328 aged 7-10 years represented 11.6% of the population in Ulanga district. Estimated population of  
48  
49 329 children aged 7-10 years from the four selected villages is 900 of which 722 (~80%) are  
50  
51 330 anticipated to participate in the survey giving a power of 85% in detecting the prevalence  
52  
53 331 between 0.8 to 2% at 5% significance level (Table 4).  
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332  
333 **Table 4. Estimated number of children aged 7 to 10 years old in the study villages in the**  
334 **Ulanga district, Tanzania, in 2016.**

Name of Village	Population size (2016)	Estimated Population aged 7-10 yrs	Estimation of participating children (80%)
Mdindo	1536	178	143
Vigoi**	2572	298	239
Misegezi	3658*	424*	340*
<b>Total</b>	<b>7766</b>	<b>900</b>	<b>722</b>

335  
336 **Data collection procedures**  
337 Data collection will be done using tablet computers. All data collection forms will be developed in  
338 the open source software 'Open Data Kit' (ODK, <https://opendatakit.org/>). Interviewers will be  
339 trained in how to perform tablet computer based surveys. A technical data coordinator will be  
340 assigned to guarantee completeness and quality of data, and to assure daily data transfer from  
341 each tablet computer to the central server for data security.

#### 342 **Data management and analysis**

343 The prevalence of epilepsy and NS will be computed as a ratio of the number of epilepsy and NS  
344 cases per total number of people registered in the households visited. The incidence of new  
345 cases of epilepsy is defined as the number of persons who developed epileptic seizures within  
346 two years preceding the study, divided by twice the population size, assuming that the change in  
347 population within the two years has a minimal effect on the incidence. Prevalence and incidence  
348 will be compared between villages and to the 1989 data. Ivermectin treatment coverage and  
349 onchocerciasis prevalence will be calculated. Demographic and clinical characteristics of persons  
350 with epilepsy having a positive Ov16 serology will be compared to epilepsy cases with negative  
351 Ov16 serology. Ivermectin treatment coverage, epilepsy prevalence and incidence and OV16  
352 positivity rate among children 7-10 years old will be compared among villages, weighted for the

1  
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3 353 difference in population size between villages. Odds ratios will be calculated for epilepsy cases  
4  
5 354 with positive Ov16 results, and the association of Ov16 positivity and epilepsy will be analysed by  
6  
7 355 age group.  
8

9 356

## 11 357 **Ethics**

13 358 The protocol has received ethical approval from the ethics committee of the University of  
14  
15 359 Antwerp, Antwerp, Belgium (29.08.2016) and the National Institut of Medical Research (NIMR)  
16  
17 360 ethical committee Dar es Salaam, Tanzania (24.08.2016). Before the activities start, the research  
18  
19 361 team will hold meetings with community leaders and health workers of the selected villages. The  
20  
21 362 procedure, purpose and specific aim of the present study will be explained and discussed in  
22  
23 363 regard to the potential risks and benefits for the community. Community leaders, village health  
24  
25 364 workers and researcher will maintain the initially established communication for the entire  
26  
27 365 duration of the study. The dissemination of results will be organized in a similar way as the initial  
28  
29 366 meeting.

31  
32 367 As approved by the relevant ethics committees, only participants who provide written informed  
33  
34 368 consent will be enrolled in the study. Participant information sheets and consent forms will be  
35  
36 369 available in English and Kiswahili. In case of illiteracy, information sheets and consent forms will  
37  
38 370 be read to the participant in the presence of a witness. All participants are permitted to withdraw  
39  
40 371 from the study activities, without reason, at any time. All personal information, samples and test  
41  
42 372 results will be encoded and treated confidentially. People identified with untreated epilepsy or  
43  
44 373 with interrupted treatment will be referred to the treatment centre and receive advice for care and  
45  
46 374 support.

## 49 375 **Data storage and handling**

51 376 All data files will be centralised and stored in a secured central server. Name-linked information  
52  
53 377 on participants and ID codes will remain confidential and will be used only to communicate  
54  
55 378 clinical results to participants for their respective treatments.  
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5 380 **DISCUSSION**

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7 381 The central research question of this study is to determine whether mass drug administration of  
8  
9 382 ivermectin using the CDTI methodology has the potential to prevent the onset of onchocerciasis  
10  
11 383 associated epilepsy. The expected results will contribute to a better understanding of the linkage  
12  
13 384 between the onset of epilepsy and NS in particular, onchocerciasis and the impact of CDTI. In  
14  
15 385 northern Uganda, an NS epidemic stopped after introducing a programme combining CDTI and  
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17 386 larviciding of the main rivers. This study will be the first to investigate systematically whether  
18  
19 387 CDTI alone may reduce epilepsy in an onchocerciasis endemic region.

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21  
22 388 With the Ov16 serological survey among children between the ages 7-10 we will be able to  
23  
24 389 estimate the ongoing transmission of onchocerciasis in the Mahenge area after 20 years of CDTI.

25  
26 390 So far, the onchocerciasis control program in the study area was monitored based on annual  
27  
28 391 ivermectin treatment coverage data provided by the community directed distributors of  
29  
30 392 ivermectin. With this study we will obtain ivermectin treatment coverage data by interviewing the  
31  
32 393 population. Moreover, by performing an Ov16 seroprevalence study among children under the  
33  
34 394 age of 10 years we will obtain a real-time estimate of the level of ongoing transmission of  
35  
36 395 onchocerciasis. Hopefully, results will show a low Ov16 seroprevalence in children and a  
37  
38 396 decreased prevalence of epilepsy since 1989. In case a high Ov16 seroprevalence is found this  
39  
40 397 will suggest that the CDTI programme was performing suboptimal and/or that ivermectin  
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42 398 resistance may have developed. It may also indicate that CDTI should be combined with  
43  
44 399 larviciding rivers to reduce blackfly abundance. There is a possibility that we may not be able to  
45  
46 400 show an impact of CDTI because in case of high level exposure to infectious blackflies the  
47  
48 401 administration of ivermectin only once a year may not be sufficient to decrease onchocerciasis  
49  
50 402 transmission considerably. Moreover in pre- and post-CDTI comparison it is possible that  
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52 403 observed differences in epilepsy prevalence and incidence are not related to the intervention  
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54 404 (CDTI) but to some of the other factors (e.g. those mentioned in Fig. 1) that might have changed

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3 405 over time. However, a site visit to the Mahenge study site revealed that the village population had  
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5 406 increased by a factor of 3, but there was no important in- or out migration or any other major  
6  
7 407 change in lifestyle of the population or another major environmental change. In all the villages  
8  
9 408 included in the study, such potential changes will be carefully assessed to control for potential  
10  
11 409 confounding factors. Families who migrated into the study area after the implementation of CDTI  
12  
13 410 will not be included in the analyses.

### 15 411 **Outlook**

17 412 This study aims to unravel the potential impact of CDTI on reducing the incidence of epilepsy in  
18  
19 413 onchocerciasis endemic areas. The results will provide an evidence base to strengthen CDTI  
20  
21 414 programs for the elimination goal for onchocerciasis and that has the power to prevent new  
22  
23 415 cases of epilepsy associated to onchocerciasis. The results and lessons learned from this study  
24  
25 416 will be disseminated by publications in open access journals, as well as presentations at scientific  
26  
27 417 conferences and shared with all interested health authorities in Tanzania and beyond.

30 418

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35  
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37  
38 422 during our visit and for their input that provided background information and practical  
39  
40 423 considerations for the development of the current study protocol.

43 424

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### 28 29 595 **Authors' contribution**

30  
31 596 All listed authors contributed to the development of the study design, essential study documents  
32  
33 597 and study tools. According to their different areas of expertise, the authors critically revised  
34  
35 598 specific parts of this manuscript: HG wrote the manuscript; HG, BM, PS, RC developed the study  
36  
37 599 protocol; WM, MM, WM developed and approved the neurological study protocol and the survey  
38  
39 600 tools; HG, BM, AK, developed the methodology and tools for the digital data collection; HG, BM,  
40  
41 601 RC visited the study sites.  
42  
43

### 44 602 **Data sharing statement**

45  
46 603 Data will be available from the Global Health Institute of the University of Antwerp at  
47  
48 604 [https://pintra.uantwerpen.be/webapps/cmsmain/webui/\\_xy-914103\\_1-t\\_KW7pxaf1](https://pintra.uantwerpen.be/webapps/cmsmain/webui/_xy-914103_1-t_KW7pxaf1)  
49

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51  
52 606 This research is embedded in a five country research project on epilepsy, nodding syndrome and  
53  
54 607 onchocerciasis entitled 'NSETHIO', and receives funding from the European Research Council,  
55  
56 608 Advanced Grant (ERC-2014-ADG), grant No.671055.  
57

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2  
3 609 **Competing interests**  
4

5 610 The authors declare that they have no competing interests.  
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7 611  
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9 612  
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13

14 614 **Figure caption**  
15

16 615 **Figure 1.** There is an extensive network of controllable and uncontrollable factors influencing the  
17  
18 616 level of onchocerciasis endemicity and prevalence and incidence of associated epilepsy.  
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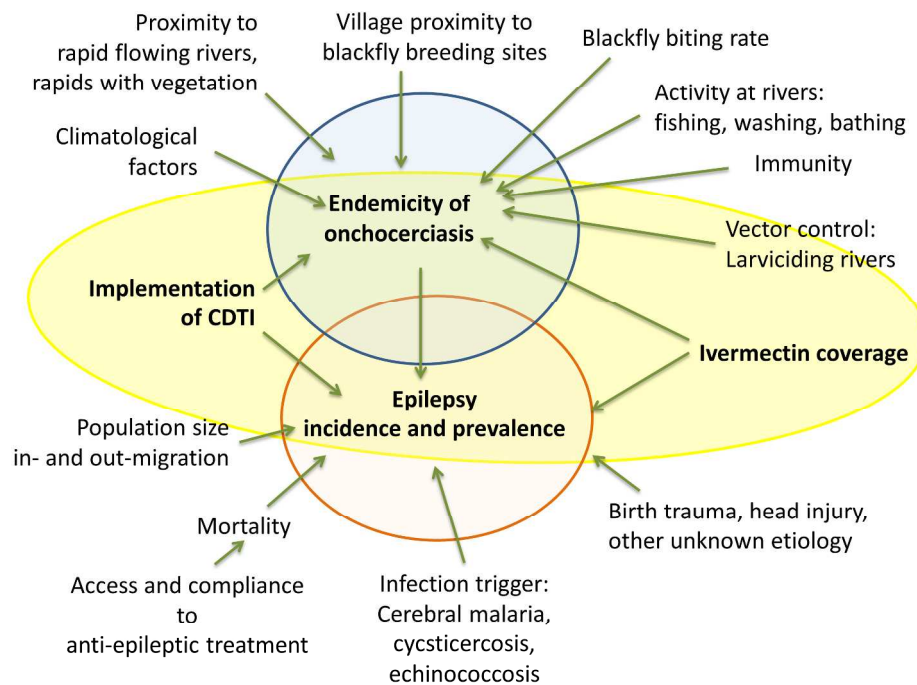


Figure 1. There is an extensive network of controllable and uncontrollable factors influencing the level of onchocerciasis endemicity and prevalence and incidence of associated epilepsy.

254x190mm (300 x 300 DPI)



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6 **1 SUPPLEMENTARY ANNEX**

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9  
10 **3 5 QUESTIONS TARGETED FOR THEW SCREENING OF EPILEPSY CASES**  
11  
12 *If at least one of the 5 questions is answered with YES, the person will be invited to participate in*  
13 *the neurological examination for case verification.*  
14  
15

16  
17  
18 **7 QUESTION 1**

19  
20  
21 Have you ever lost consciousness and experienced:

22  
23 a) Loss of bladder control?  YES  NO  DON'T KNOW

24  
25 b) Foam at the mouth?  YES  NO  DON'T KNOW  
26  
27

28  
29 **12 QUESTION 2**

30  
31 Have you ever experienced absence(s) or sudden loss(es) of contact with the surroundings, for a  
32  
33 short duration of time?  YES  NO  DON'T KNOW  
34  
35

36  
37 **16 QUESTION 3**

38  
39 Have you ever experienced sudden, uncontrollable twitching or shaking of your arms, legs or  
40  
41 head, for a period of a few minutes?  YES  NO  DON'T KNOW  
42  
43

44  
45 **20 QUESTION 4**

46  
47 Do you sometimes experience sudden and brief bodily sensations, see or hear things that are not  
48  
49 there, or smell strange odours?  YES  NO  DON'T KNOW  
50  
51

52  
53 **24 QUESTION 5**

54  
55 Have you ever been told that you are suffering from epilepsy or that you have already had  
56  
57 epileptic fits?  YES  NO  DON'T KNOW  
58  
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# BMJ Open

## Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for onchocerciasis, and the potential impact of community-directed treatment with ivermectin: a cross sectional study and comparison over 28 years

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Manuscripts

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3 1 **Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for**  
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5 2 **onchocerciasis, and the potential impact of community-directed treatment with**  
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7 3 **ivermectin: a cross sectional study and comparison over 28 years**  
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9 4

11 5 Helena Greter<sup>a\*</sup>, Bruno Mbando<sup>b</sup>, Williams Makunde<sup>b</sup>, Mohamed Mnacho<sup>c</sup>, William Matuja<sup>c</sup>,  
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## 17 **ABSTRACT**

### 18 **Introduction**

19 Worldwide, there are an estimated 50 million people affected by epilepsy. Its etiology is manifold,  
20 and parasitic infections play an important role, specifically onchocerciasis. From onchocerciasis  
21 endemic areas a distinctive form of epilepsy has been described as nodding syndrome, affecting  
22 children and causing nodding seizures, mental retardation and debilitating physical development.  
23 Onchocerciasis is treatable with ivermectin. Control programs using community directed  
24 treatment with ivermectin (CDTI) are implemented in endemic countries. This study is designed  
25 to contribute to a better understanding of the linkage between the onset of epilepsy,  
26 onchocerciasis and CDTI. Comparing the epidemiological data on epilepsy and onchocerciasis  
27 from pre-CDTI and 20 years after its introduction will allow identifying a potential impact of  
28 ivermectin on the onset of epilepsy.

### 29 **Methods and analysis**

30 The study will be conducted in the Mahenge highlands in Tanzania. Study site selection is based  
31 on an in-depth study on epilepsy in that area dating from 1989. CDTI was introduced in 1997. By  
32 a door-to-door approach, the population will be screened for epilepsy using a validated  
33 questionnaire. Suspected cases will be invited for a neurological examination for case  
34 verification. Onchocerciasis prevalence will be assessed by a rapid epidemiological assessment  
35 for prevalence. As an indicator for ongoing transmission, children younger than 10 years of age  
36 will be tested for Ov16 antibodies. Ivermectin use will be assessed at household level. Epilepsy  
37 data will be analysed in comparison to the 1989 data to reveal pre- and post-CDTI  
38 implementation prevalence and incidence.

### 39 **Ethics and dissemination**

40 The protocol has received ethical approval from the ethics committees of the University of  
41 Antwerp, Belgium and of the National Institut of Medical Research (NIMR), Dar es Salaam,

1  
2  
3 42 Tanzania. The findings will be published in peer-reviewed journals, and presented to the health  
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5 43 authorities in Tanzania, at national, regional and village level.  
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9 45 **Strengths and limitations of this study:**

- 10  
11 46 • This study will allow comparison of large scale population based data on epilepsy  
12  
13 epidemiology in Mahenge over a period of 28 years.  
14  
15 47  
16 48 • The strength of the study is that it is a first study to follow-up epilepsy epidemiology in the  
17  
18 Mahenge area since the introduction of community directed treatment with ivermectin.  
19  
20 49  
21 50 • Comparaision of the data obtained in 1989 and 2017 will be challenged by the slightly  
22  
23 different study methodologies used.  
24  
25 51  
26 52 • The study design is limited in accounting for potential confounding factors other than CDTI  
27  
28 that may influence epilepsy incidence and prevalence.  
29  
30 53  
31 54 • Focusing on villages with high epilepsy burden in the past may lead to an overestimation of  
32  
33 the potential impact of CDTI.  
34  
35 55

36  
37 56  
38  
39 57 **Key words**

40  
41 58 Epilepsy  
42  
43 59 Nodding disease  
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45 60 Onchocerciasis  
46  
47 61 Ivermectin  
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49 62 Tanzania  
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53 64 **INTRODUCTION**

54  
55 65 **Epilepsy in onchocerciasis endemic regions in Africa**

56  
57 66 Epilepsy is a chronic disease estimated to affect 50 million people worldwide according to World  
58  
59 67 Health Organisation (WHO).<sup>1</sup> In general, higher prevalence and incidence are reported from  
60

1  
2  
3 68 those populations living in low and middle income countries (LMICs) when compared to  
4  
5 69 industrialized countries.<sup>2 3</sup> In fact, more than 85% of the global burden of epilepsy occurs in the  
6  
7 70 people living in LMICs.<sup>4 5</sup> The etiology of epilepsy is very diverse and not yet fully understood.  
8  
9 71 Besides birth trauma and head injury involving the brain, infectious diseases can trigger epilepsy  
10  
11 72 as well. Several parasitic infections are associated with epilepsy such as cerebral malaria,  
12  
13 73 neurocysticercosis, echinococcosis, and onchocerciasis.<sup>6-8</sup> Many of these epilepsy cases could  
14  
15 74 be prevented through timely anti-parasitic treatment. Epilepsy manifests in a variety of seizure  
16  
17 75 types and degrees of intensity.<sup>9</sup> In the 1960 in Tanzania, Aall-Jillek was the first to describe an  
18  
19 76 unusual form of epileptic seizures characterized by nodding movements of the head.<sup>10 11</sup> Later,  
20  
21 77 this distinct form of epilepsy has been described also in Uganda and South Sudan, and has been  
22  
23 78 named as nodding syndrome (NS).<sup>12 13</sup> NS is a debilitating epileptic disorder mainly affecting  
24  
25 79 children at the ages of 3 and 18 years.<sup>14</sup> The seizures are characterized by a brief loss of  
26  
27 80 muscle-tone in the neck, leading to repetitive head-nodding.<sup>15</sup> NS is often associated with  
28  
29 81 cognitive decline, and sometimes with stunted growth.<sup>16</sup> So far, NS is solely described in  
30  
31 82 onchocerciasis endemic areas.<sup>12</sup> A NS epidemic has been observed in the past two decades in  
32  
33 83 northern Uganda and in neighboring South Sudan.<sup>17 16</sup> The weight of the public health burden  
34  
35 84 caused by epilepsy in onchocerciasis endemic regions can be illustrated by the situation in the  
36  
37 85 West Equatorial State in South Sudan, where in the village of Mvolo, over 50% of the families  
38  
39 86 had at least one child with epilepsy, resulting in one in six children of the village suffering from  
40  
41 87 epilepsy.<sup>18</sup>  
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44  
45 88 Health systems services in remote rural regions in Africa are rarely capable to provide continuous  
46  
47 89 anti-epileptic treatment to those patients in need.<sup>5</sup> Further more, most health care workers lack  
48  
49 90 training to diagnose and treat persons with epilepsy adequately. In many societies in Africa, and  
50  
51 91 in addition to the clinical burden, epilepsy is perceived as a possession by evil spirits and hence  
52  
53 92 bears a stigma that puts the diseased individual and his family at risk for social isolation.<sup>19</sup>  
54  
55 93 Moreover, the family's economy is negatively impacted by the disease, since an epileptic family

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3 94 member needs specific care and supervision, detaching care takers from their subsistence  
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5 95 duties.<sup>20</sup>  
6  
7 96 NS only occurs in onchocerciasis endemic areas. An epidemiological association between  
8  
9 97 epilepsy and onchocerciasis was first reported from western Uganda in the early 1990s.<sup>21 22</sup> A  
10  
11 98 case-control study performed in 1991-92 in the Mbam valley in Cameroon demonstrated a  
12  
13 99 significantly higher microfilarial load in persons with epilepsy than in controls.<sup>23</sup> Study results from  
14  
15 100 other onchocerciasis-endemic African countries underline this association.<sup>8 24</sup> To describe this  
16  
17 101 epidemiological phenomenon the term onchocerciasis associated epilepsy (OAE) was proposed  
18  
19 102 by Kaiser and colleagues.<sup>24</sup> Case-control studies in northern Uganda and South Sudan focusing  
20  
21 103 on NS patients produced similar results, showing a higher prevalence of onchocerciasis in NS  
22  
23 104 cases compared to non-epileptic controls.<sup>16 17</sup> It is, however, unclear how onchocerciasis might  
24  
25 105 cause NS. Although the eye and the optical nerve are affected when onchocerciasis causes  
26  
27 106 blindness, microfilariae and adult *Onchocerca volvulus* worms are not generally considered to be  
28  
29 107 able to invade the central nervous system. Recent research hypothesises that an immunological  
30  
31 108 cross-reaction of onchocerciasis-specific antibodies may provoke a neurotoxic reaction and  
32  
33 109 trigger NS.<sup>25</sup>  
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### 39 111 **Onchocerciasis, a treatable neglected tropical disease facing obstacles on the road to** 40 41 112 **elimination**

42  
43 113 Onchocerciasis is a parasitic disease caused by an infection with the the worm *O. volvulus*  
44  
45 114 whose filarial larvae are transmitted by blackflies (*Simuliidae* spp.). In the final host, humans, the  
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47 115 adult female worms encapsulate in the subcutaneous tissue forming visually detectable nodules.  
48  
49 116 Each female worm releases up to one thousand microfilariae per day. These microfilariae  
50  
51 117 provoke itching, dermatitis and – if left untreated – blindness, which led to the disease also being  
52  
53 118 called river blindness. Blackflies get infected with microfilariae when biting infected humans in  
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55 119 proximity to fast flowing rivers, the breeding site of the blackflies. After passing through several  
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3 120 larval stages, infected blackflies spread the parasite by biting other people. Onchocerciasis is  
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5 121 treatable with ivermectin.<sup>26</sup> The drug has a twofold mechanism of action: (i) it kills the  
6  
7 122 microfilariae and (ii) inhibits their release by the adult female worm for up to two years after a  
8  
9 123 single dose treatment.<sup>27</sup> Hence, ivermectin has a strong impact on reducing transmission.  
10  
11 124 However, ivermectin is not lethal to adult worms and infected persons have to take it annually for  
12  
13 125 up to 15 years.<sup>28</sup> Onchocerciasis is a priority disease scheduled for elimination by 2025 by the  
14  
15 126 WHO. Today, 99% of the globally 37 million people infested live in Africa.<sup>1</sup> In 1995, the African  
16  
17 127 Program for Onchocerciasis Control (APOC) was initiated for the implementation of the  
18  
19 128 onchocerciasis control programme based on community directed treatment with ivermectin  
20  
21 129 (CDTI). APOC was coordinating these activities in endemic areas of 22 African countries.<sup>29</sup> Since  
22  
23 130 May 2016, CDTI control programmes are integrated in the WHO Expanded Special Project for  
24  
25 131 Elimination of Neglected Tropical Diseases (ESPEN).<sup>30</sup> CDTI overcomes the limited performance  
26  
27 132 of weak health systems in rural areas by using an active, strategic involvement of the  
28  
29 133 community.<sup>31</sup> To reach the entire population, ivermectin distribution is organized by trained  
30  
31 134 volunteers in each village, resulting in a large geographical coverage. CDTI, in certain regions  
32  
33 135 combined with the control of the blackfly by larviciding of breeding sites (i.e. fast flowing rivers),  
34  
35 136 resulted in a measurable impact reflected by a remarkable transmission reduction in the past 20  
36  
37 137 years.<sup>32</sup> But success and effectiveness of these targeted interventions lack comprehensiveness.  
38  
39 138 Certain onchocerciasis endemic regions remain undersupplied or unreachable for CDTI due to  
40  
41 139 political instability, insecurity or armed conflicts.<sup>33</sup> As a consequence in the war-affected regions  
42  
43 140 of South Sudan and northern Uganda, onchocerciasis control measures were stopped or  
44  
45 141 implementation started only recently. Moreover, misconceptions and the fear of adverse effects  
46  
47 142 result in suboptimal therapeutic coverage and reduce the effectiveness of the control program.<sup>34</sup>  
48  
49 143 Adding to the complexity of onchocerciasis control, in regions where *Loa loa* and onchocerciasis  
50  
51 144 are co-endemic, ivermectin may cause severe adverse effects (encephalopathy, coma or death)  
52  
53 145 in infected individuals harbouring a high *Loa loa* microfilariae load.<sup>35</sup> <sup>36</sup> Thus, CDTI  
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3 146 implementation in such regions requires additional precautions.<sup>37</sup> This is the case in certain  
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5 147 regions of Cameroon and the Democratic Republic of Congo (DRC).<sup>38</sup> Compliance to CDTI  
6  
7 148 programs can also decrease over the years since less direct positive effects can be observed  
8  
9 149 when onchocerciasis prevalence drops, and healthy feeling people may not appreciate the  
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11 150 importance of continuing repeated treatment.<sup>39</sup>  
12

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16 152 **The potential of CDTI to reduce the incidence of epilepsy in onchocerciasis endemic**  
17  
18 153 **regions**

19  
20 154 The endemicity of onchocerciasis and the prevalence and incidence of epilepsy are influenced by  
21  
22 155 a multitude of factors (Figure 1). These factors are of uncontrollable nature (climate,  
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24 156 environment, ecology), and of controllable nature (prevention and intervention programs, access  
25  
26 157 to health care and treatment).  
27

28 158  
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30 159 <<<<<Figure 1 near here>>>>>>>>  
31

32 160  
33  
34 161 The two heavily affected regions of the last decades, Northern Uganda and South Sudan, were –  
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36 162 and South Sudan still is - affected by armed conflicts. In 2012, after the conflict ended in northern  
37  
38 163 Uganda, the NS epidemic was investigated. Following on, epilepsy treatment was provided,  
39  
40 164 biannual CDTI was implemented and larviciding of major rivers was carried out.<sup>40</sup> Since 2013 the  
41  
42 165 NS epidemic in northern Uganda has reportedly been halted.<sup>41</sup> In contrast in South Sudan, where  
43  
44 166 CDTI was stopped because of insecurity, new cases of NS continue to appear.<sup>18</sup> Based on the  
45  
46 167 observations from northern Uganda, it has been suggested that ivermectin may reduce the  
47  
48 168 incidence of NS and other forms of epilepsy in onchocerciasis endemic areas.<sup>42</sup> Considering that  
49  
50 169 30% of the globally 37 million individuals infected with onchocerciasis do not have access to  
51  
52 170 effective treatment, and that 1% of those develop epilepsy (equivalent to the estimated excess  
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171 prevalence of epilepsy over non-onchocerciasis areas) the number of excess cases of epilepsy  
 172 attributed to onchocerciasis most likely exceeds 100'000.<sup>1 7</sup>

173 Recent observations in the DRC and northern Uganda suggest that optimal treatment coverage  
 174 of ivermectin may stop the incidence of NS and other forms of OAE.<sup>42</sup>

175

## 176 **Aim**

177 The population based study from 1989 by Rwiza et al. established the baseline prevalence of all  
 178 forms of epilepsy in the Ulanga district, Tanzania.<sup>43</sup> With this 2017 population based study, we  
 179 aim to further evaluate the prevalence and incidence rates of new epilepsy cases, including a  
 180 complete case ascertainment of all forms of epilepsy encountered, and compare the data to the  
 181 1989 data (Table 1).

182

183 **Table 1. The pre- and post-CDTI epilepsy study periods and estimated epilepsy prevalence**  
 184 **and incidence in the Mahenge area, Ulanga district in Tanzania.**

Mahenge area, Ulanga district, Tanzania		
Year of epilepsy study data collection	1989 <sup>43</sup>	2017
Status of CDTI at study year	Pre-CDTI	Post-CDTI (ongoing since 1997)
Estimated epilepsy prevalence	20.2/1'000	14/1'000*
Estimated epilepsy incidence	146/100'000	81.7/100'000**

185 \*Median epilepsy prevalence and \*\*incidence in low and middle income countries<sup>4 3</sup>

186

## 187 **Objective**

188 The main objective of this study is to identify the potential impact of long-term onchocerciasis  
 189 control using CDTI on the prevalence and incidence of epilepsy in selected villages in the  
 190 Mahenge area of the Ulanga district in Tanzania.

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5 192 **Specific objectives**  
6  
7 193 1. To determine the prevalence of all forms of epilepsy in selected villages of the Mahenge area  
8  
9 194 and compare the related data from 2017 to the 1989 data.  
10  
11 195 2. To determine the incidence rate of annual new onset cases of all forms of epilepsy in the  
12  
13 196 Mahenge area and compare the related data from 2017 to the 1989 data.  
14  
15 197 3. To assess the ivermectin coverage and the onchocerciasis prevalence with a REMO  
16  
17 198 assessment in selected villages of the Mahenge area.  
18  
19 199 4. To determine the level of onchocerciasis transmission by a serological survey using a rapid  
20  
21 200 test among children in selected villages of the Mahenge area.  
22  
23 201 5. To investigate the potential difference in clinical appearance of epilepsy in patients with  
24  
25 202 negative onchocerciasis serology to patients with positive onchocerciasis serology.  
26  
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28 203

## 204 **METHODS AND ANALYSIS**

205 The study consists of two parts: (I) a study to determine the prevalence and incidence of epilepsy  
206 and (II) a study to determine ivermectin coverage, onchocerciasis prevalence and level of  
207 transmission. Data collection was carried out between January and September 2017. Analysis is  
208 planned to be finalized by end of 2017, to allow publishing of the results in 2018.

### 209 **Study site**

210 The study is taking place in the Mahenge area of the Ulanga district, Morogoro region in south-  
211 eastern Tanzania, a mountainous area with fast flowing rivers.

### 212 **Epilepsy in the Mahenge area**

213 In the 1960s, Aall-Jilnek was the first to report a high burden of epilepsy in the Mahenge area,  
214 and also described the first NS cases.<sup>10</sup> In 1989, Rwiza et al. carried out a population based  
215 survey to determine prevalence and incidence of epilepsy in the Ulanga district and found an  
216 annual incidence of 73.3 new cases in 100'000. The prevalence was 10.2 cases in 1000, and

varied between villages from 5.1 to 37.1 cases in 1'000. Those villages with the highest prevalence were located in the Mahenge highlands (Table 2).<sup>43</sup>

**Table 2. Population size and prevalence of epilepsy in some villages of the Ulanga district, Tanzania, showing the highest prevalence in 1989, as reported by Rwiza et al. in 1992**

Name of Village	Population size	Number of Epilepsy cases	Prevalence per 1000 people
Sali <sup>δ</sup>	1'282	14	10.9
Mdindo <sup>δ</sup>	539	20	37.1
Vigoi <sup>δ</sup>	1'822	23	12.6
Lupiro	1'697	17	10
Misegezi	1'667	18	10.8
<b>Total</b>	<b>7'007</b>	<b>92</b>	<b>13.13</b>

<sup>δ</sup>Located in Mahenge highlands

### Onchocerciasis and CDTI in the Mahenge area

The Morogoro region is among the five regions where onchocerciasis is endemic in Tanzania. The region presents four foci: Uluguru mountain, Ulanga/Mahenge, Kilosa and the Nguru mountain foci.<sup>44</sup> The Ulanga district, specifically the Mahenge area, was known for its high endemicity of onchocerciasis since the early last century.<sup>45</sup> Mass drug administration using annual CDTI was introduced in the Mahenge area in 1997.<sup>46</sup> Before CDTI was implemented, 58.6% of a sample of 482 inhabitants of the Mahenge area were found to have a microfilariae positive skin snip.<sup>47</sup> Twelve years later (in 2009) the rapid epidemiological mapping of onchocerciasis (REMO) in 10 villages in the Mahenge area revealed that the percentage of persons with a microfilariae positive skin snip has dropped to 21.9%, with a mean village prevalence of 8.3%.<sup>32</sup>

### Study population

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3 235 The three villages Mdingo, Vigoi and Mizegezi that had high epilepsy prevalence during the 1989  
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5 236 study will be selected for this study.<sup>43</sup> The entire population of each of these villages will be  
6  
7 237 included in the study.  
8

9 238

## 11 239 **Epilepsy and NS prevalence / incidence study**

### 13 240 **Study design**

15 241 The study is designed as a population-based cross-sectional study, following a two-stage  
16 242 approach for epilepsy case identification at village level. The gold-standard in neuro-  
17 243 epidemiological surveys to identify epilepsy cases in LMICs, the door-to-door approach, will be  
18 244 applied.<sup>48</sup> All inhabitants of the selected villages will be eligible for participation and will be  
19 245 included in the questionnaire screening survey. Due to well described limitations of questionnaire  
20 246 studies on epilepsy (stigma leading to concealment of cases, recall bias, absence of clear  
21 247 terminology for epilepsy and seizures) and to increase sensitivity of case ascertainment, key  
22 248 informants who are likely to be aware of persons with epilepsy in the village will additionally be  
23 249 consulted.<sup>3 48</sup> These may be health workers, traditional healers, teachers, or community  
24 250 leaders.<sup>49</sup>

26 251 In a second stage, persons with suspected epilepsy identified during the household screening  
27 252 survey will be further invited for clinical examination by a neurologist. The examination will  
28 253 include neurological tests and a detailed interview for case verification. In verified epilepsy cases  
29 254 the onset of the seizures will be determined and possible etiologic factors will be investigated,  
30 255 such as birth trauma, head injury, meningo-encephalitis, cerebral malaria, neurocystocercosis,  
31 256 and the history of onchocerciasis. For persons with suspected epilepsy their serological status  
32 257 will be determined using onchocerciasis rapid diagnostic test (Ov16 RDT) (Standard diagnostics,  
33 258 Inc., Gyeonggi-do, Republic of Korea).

### 35 259 **Sample size calculation**

260 According to Rwiza et al. (1992) the average prevalence of epilepsy in five villages with high  
 261 prevalence was 1.313% (Table 2). If we assume a reduction in the prevalence by 33.3% to be  
 262 able to compare the prevalence at a power of 80% and 95% confidence level, the minimal  
 263 sample size of 4,746 individuals will be required. Assuming a participation of 80%, a minimum  
 264 source population of 5,933 is necessary to obtain optimal sample size.  
 265 Since 1989 the population in the villages with high epilepsy prevalence has increased (Table 3).  
 266 For this survey we will include only the population of the villages with the highest epilepsy  
 267 prevalence in 1989. The total population of the selected villages of Mdindo, Vigoi and Misegezi in  
 268 2016 is about 7,766.

270 **Table 3. List of the study villages in the Mahenge highlands, Tanzania, and their**  
 271 **population size in 1989 and in 2016.**

Name of Village (1989)	Population size (1989)	Population size (2016)
Mdindo	539	1'536
Vigoi	1'822	2'572
Misegezi	1'667	3'658*
<b>Total</b>	<b>4'028</b>	<b>7'766</b>

\*Population projection based on the growth rate of Vigoi village

### 273 Data collection at community level

274 The community survey will commence by a questionnaire interview with the village authorities on  
 275 demographic topics, and with village health workers to address general questions on the status  
 276 of epilepsy and epilepsy treatment in the village. A complete door-to-door active screening for  
 277 persons with suspected epilepsy at village level will be performed. The interview team will be  
 278 trained on how to conduct the active search for epilepsy cases using a pre-tested, validated  
 279 screening questionnaire targeting epilepsy by 5 specific questions (provided in the  
 280 supplementary material).<sup>50 51</sup> For validation, the questionnaire will be translated to Kiswahili,

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2  
3 281 pretested and retranslated to English. The locally used terms for the two respective conditions  
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5 282 will be used (epilepsy: *kifafa*, NS: *kusinzia kichwa*). To ascertain completeness and to ensure the  
6  
7 283 best collaboration with the village population, the interviewer team will be accompanied to all  
8  
9 284 households by local village health workers. The geographical coordinates of the participating  
10  
11 285 households will be collected for the mapping and geospatial analysis of cases (proximity to rivers,  
12  
13 286 potential clustering).

### 15 287 **Case verification and validation**

16  
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18 288 All persons with suspected epilepsy identified during the door-to-door survey will be verified by a  
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20 289 neurologist. The neurologist will perform a detailed anamnesis on all persons with suspected NS  
21  
22 290 and epilepsy. In case of confirmation of the epilepsy, the neurologist will perform a medical  
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24 291 examination and administer a detailed questionnaire on the type of epilepsy. Newly diagnosed  
25  
26 292 epilepsy cases will be referred to an epilepsy treatment centre. In case the person is already  
27  
28 293 followed in a treatment centre, permission will be asked to review the medical information  
29  
30 294 available in the treatment centre to record epilepsy diagnosis and epilepsy treatment history.

### 32 295 **Definitions:**

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35 296 - A case of epilepsy will be defined according to the International League Against Epilepsy  
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37 297 (ILAE) guidelines as a patient who had at least two times nonfebrile seizures unrelated to  
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39 298 any acute metabolic disorder or to withdrawal of alcohol or drugs., lost consciousness  
40  
41 299 with convulsions with a minimal time difference of 24h between the two events.<sup>52</sup>  
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43 300 - A case will be considered as active epilepsy if the patient is receiving epilepsy treatment  
44  
45 301 or, if without anti-epileptic treatment, the patient presented at least one seizure during the  
46  
47 302 last 5 years.  
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49 303 - A case of suspected NS will be defined as a person who presented with episodes of  
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51 304 decreased consciousness during which the head dropped forward repeatedly.  
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53 305 - New cases of epilepsy will be defined as cases that appeared within the last 12 month  
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55 306 proceeding the study period.

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3 307 To allow for comparison, the epilepsy case definition applied here is identical to the definition  
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5 308 applied in 1989 by Rwiza *et al.*<sup>43</sup>  
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## 9 310 **Onchocerciasis prevalence study**

### 11 311 **Study design**

13 312 This study includes two approaches. In one approach, the aim is to determine the onchocerciasis  
14 313 prevalence in the selected villages after 20 years of CDTI by performing the WHO proposed  
15 314 REMO methodology.<sup>53</sup> In brief, in each study village, 50 adults aged at least 20 years old and  
16 315 resident in the community for at least 10 years will be invited to participate. They will be  
17 316 examined for the presence of onchocerciasis nodules (subcutaneous nodules or deep, painless,  
18 317 firm, mobile nodules over bony prominences: pelvic girdle, costal grid, knees, and skull).  
19 318 Although pre-control onchocerciasis prevalence data from the study villages is not available, a  
20 319 study from 1966 carried out in three villages in Mahenge found a skin snip positivity rate of 43%,  
21 320 60% and 65%, respectively.<sup>54</sup>  
22 321

23 322 The second part aims at determining the level of transmission of onchocerciasis in the selected  
24 323 villages. Therefore, serological testing for onchocerciasis will be done in all children at ages 7-10  
25 324 years old, using the onchocerciasis specific Ov16 RDT (Standard diagnostics, Inc., Gyeonggi-do,  
26 325 Republic of Korea). According to the National Census survey in 2012, the population of children  
27 326 aged 7-10 years represented 11.6% of the population in Ulanga district. Estimated population of  
28 327 children aged 7-10 years from the four selected villages is 900 of which 722 (~80%) are  
29 328 anticipated to participate in the survey giving a power of 85% in detecting the prevalence  
30 329 between 0.8 to 2% at 5% significance level (Table 4).  
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32 331



330 **Table 4. Estimated number of children aged 7 to 10 years old in the study villages in the**  
 331 **Ulanga district, Tanzania, in 2016.**

Name of Village	Population size (2016)	Estimated Population aged 7-10 yrs	Estimation of participating children (80%)
Mdindo	1'536	178	143
Vigoi	2'572	298	239
Misegezi	3'658*	424*	340*
<b>Total</b>	<b>7'766</b>	<b>900</b>	<b>722</b>

\*Population projection based on the growth rate of Vigoi village

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### 333 **Data collection procedures**

334 Data collection will be done using numeric tablets. All data collection forms will be developed in  
 335 the open source software 'Open Data Kit' (ODK, <https://opendatakit.org/>). Interviewers will be  
 336 trained in how to perform tablet-based surveys. A technical data coordinator will be assigned to  
 337 guarantee completeness and quality of data, and to assure daily data transfer from each tablet to  
 338 the central server for data security.

### 339 **Data management and analysis**

340 The prevalence of epilepsy and NS will be computed as a ratio of the number of epilepsy and NS  
 341 cases per total number of people registered in the households visited, respectively. The  
 342 incidence of new cases of epilepsy is defined as the number of persons who developed epileptic  
 343 seizures within two years preceding the study, divided by twice the population size, assuming  
 344 that the change in population within the two years has a minimal effect on the incidence. Results  
 345 will be presented accompanied with 95% confidence interval (95%CI), and P-value<0.05 level of  
 346 significance. Prevalence and incidence will be compared between villages and to the 1989 data.  
 347 Ivermectin treatment coverage and onchocerciasis prevalence will be calculated. Proportions will  
 348 be compared using  $\chi^2$ -test, while means will be compared using t-tests. Demographic and clinical  
 349 characteristics of persons with epilepsy having a positive Ov16 serology will be compared to

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3 350 epilepsy cases with negative Ov16 serology. Ivermectin treatment coverage, epilepsy prevalence  
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5 351 and incidence and OV16 positivity rate among children 7-10 years old will be compared among  
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7 352 villages, weighted for the difference in population size between villages. Odds ratios will be  
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9 353 calculated for epilepsy cases with positive Ov16 results, and the association of Ov16 positivity  
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11 354 and epilepsy will be analysed by age group.  
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### 15 356 **Ethics**

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18 357 The protocol has received ethical approval from the ethics committee of the University of  
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20 358 Antwerp, Antwerp, Belgium (29.08.2016) and the National Institute of Medical Research (NIMR)  
21  
22 359 ethical committee Dar es Salaam, Tanzania (24.08.2016). Before the activities start, the research  
23  
24 360 team will hold meetings with community leaders and health workers of the selected villages. The  
25  
26 361 procedure, purpose and specific aim of the present study will be explained and discussed with  
27  
28 362 regard to the potential risks and benefits for the community. Community leaders, village health  
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30 363 workers and researchers will maintain the initially established communication for the entire  
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32 364 duration of the study. The dissemination of results will be organized in a similar way as the initial  
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34 365 meeting.

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37 366 As approved by the relevant ethics committees, only participants who provide written informed  
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39 367 consent will be enrolled in the study. Participant information sheets and consent forms will be  
40  
41 368 available in English and Kiswahili. In case of illiteracy, information sheets and consent forms will  
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43 369 be read to the participant in the presence of a witness. All participants are permitted to withdraw  
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45 370 from the study activities, without reason, at any time. All personal information, samples and test  
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47 371 results will be encoded and treated confidentially. People identified with untreated epilepsy or  
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49 372 with interrupted treatment will be referred to the treatment centre and receive advice for care and  
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51 373 support.

### 52 53 374 **Data storage and handling**

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3 375 All data files will be centralised and stored in a secured central server. Name-linked information  
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5 376 on participants and ID codes will remain confidential and will be used only to communicate  
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7 377 clinical results to participants for their respective treatments.  
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## 11 379 **DISCUSSION**

13 380 The central research question of this study is to determine whether mass drug administration of  
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15 381 ivermectin using CDTI has the potential to prevent the onset of OAE. The expected results will  
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17 382 contribute to a better understanding of the linkage between the onset of epilepsy and NS in  
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19 383 particular, onchocerciasis and the impact of CDTI. In northern Uganda, an NS epidemic has been  
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21 384 halted after introducing a programme combining CDTI and larviciding of the main rivers. This  
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23 385 study will be the first to investigate systematically whether CDTI alone may reduce epilepsy in an  
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25 386 onchocerciasis endemic region. To do so pre- and post-CDTI epilepsy prevalence and incidence  
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27 387 data will be compared. Concurrently, with the Ov16 serological survey among children between  
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29 388 the ages 7-10 years, we will be able to assess whether the transmission of onchocerciasis is  
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31 389 ongoing in the Mahenge area after 20 years of CDTI. So far, the onchocerciasis control program  
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33 390 in the study area was monitored based on annual ivermectin, treatment coverage data being  
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35 391 provided by the community directed distributors of ivermectin. With this study we will obtain  
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37 392 ivermectin treatment coverage data by interviewing the population. Moreover, by performing an  
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39 393 Ov16 seroprevalence study among children under the age of 10 years we will obtain a real-time  
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41 394 estimate of the level of ongoing transmission of onchocerciasis. The hypothesis is to find a low  
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43 395 Ov16 seroprevalence in children and a decreased prevalence of epilepsy since 1989. In case a  
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45 396 high Ov16 seroprevalence is found this will suggest that the CDTI programme was performing  
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47 397 suboptimal and/or that ivermectin resistance may have developed. It might therefore be useful to  
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49 398 combine CDTI with larviciding rivers to reduce blackfly abundance.  
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53 399 This study also has limitations. The methods used will not allow for measuring onchocerciasis  
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55 400 infection intensity, one of the main factors influencing the development of OAE. There is a

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3 401 possibility that it may not be possible to show an impact of CDTI because in case of high level  
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5 402 exposure to infectious blackflies the administration of ivermectin only once a year may not be  
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7 403 sufficient to decrease onchocerciasis transmission considerably. Moreover, in pre- and post-  
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9 404 CDTI comparison it is possible that observed differences in epilepsy prevalence and incidence  
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11 405 are not related to the intervention (CDTI) but to some of the other factors (e.g. those mentioned  
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13 406 in Fig. 1) that might have changed over time. However, a site visit to the Mahenge study site  
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15 407 revealed that the village population had increased by a factor of 3, but there was no important in-  
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17 408 or out migration or any other major change in lifestyle of the population or another major  
18  
19 409 environmental change. In all the villages included in the study, such potential changes will be  
20  
21 410 carefully assessed to control for potential confounding factors. Families who migrated into the  
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23 411 study area after the implementation of CDTI will not be included in the analyses.  
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## 26 412 **Outlook**

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28 413 This study aims to unravel the potential impact of CDTI on reducing the incidence of epilepsy in  
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30 414 onchocerciasis endemic areas. Study results may provide evidence that strengthening CDTI  
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32 415 programs could prevent the onset of OAE. The results and lessons learned from this study will be  
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34 416 disseminated by publications in open access journals, as well as presentations at scientific  
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36 417 conferences and shared with all interested health authorities in Tanzania and beyond.  
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39 418

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41  
42  
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44  
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46  
47 422 during our visit and for their input that provided background information and practical  
48  
49 423 considerations for the development of the current study protocol.  
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35 588  
36 589 **Authors' contribution**  
37  
38 590 All listed authors contributed to the development of the study design, essential study documents  
39  
40 591 and study tools. According to their different areas of expertise, the authors critically revised  
41  
42 592 specific parts of this manuscript: HG wrote the manuscript; HG, BM, PS, RC developed the study  
43  
44 593 protocol; WM, MM, WM developed and approved the neurological study protocol and the survey  
45  
46 594 tools; HG, BM, AK, developed the methodology and tools for the digital data collection; HG, BM,  
47  
48 595 RC visited the study sites.  
49

50 596 **Data sharing statement**  
51  
52 597 Data will be available from the Global Health Institute of the University of Antwerp at  
53  
54 598 [https://pintra.uantwerpen.be/webapps/cmsmain/webui/\\_xy-914103\\_1-t\\_KW7pxaf1](https://pintra.uantwerpen.be/webapps/cmsmain/webui/_xy-914103_1-t_KW7pxaf1)  
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4  
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8

9 603 **Competing interests**

10  
11 604 The authors declare that they have no competing interests.  
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19  
20 608 **Figure caption**

21  
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23 609 **Figure 1.** Onchocerciasis endemicity and prevalence and incidence of associated epilepsy are  
24  
25 610 influenced by an extensive network of controllable and uncontrollable factors.  
26  
27 611

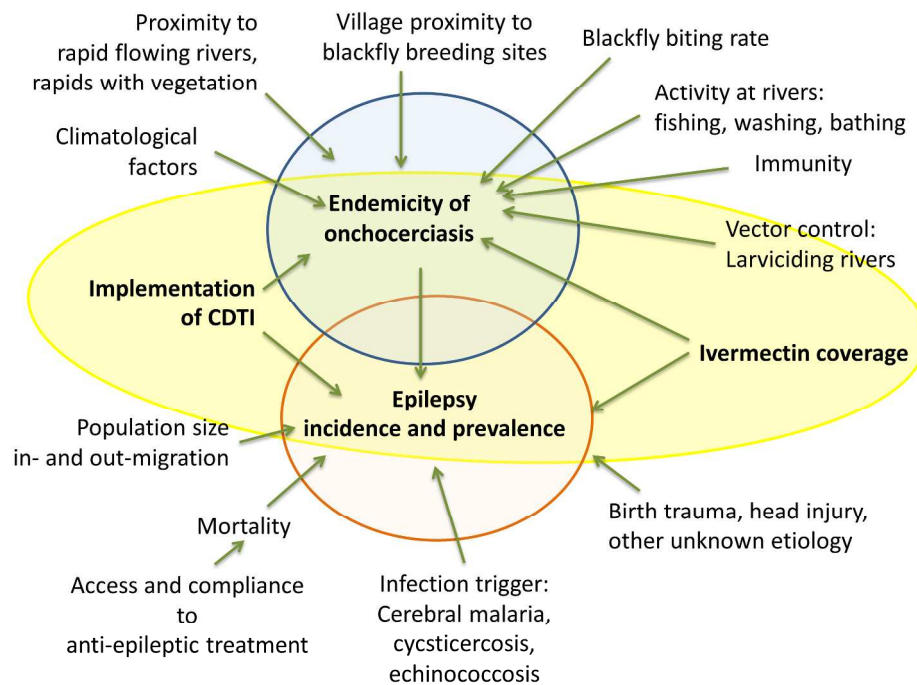


Figure 1. There is an extensive network of controllable and uncontrollable factors influencing the level of onchocerciasis endemicity and prevalence and incidence of associated epilepsy.

254x190mm (300 x 300 DPI)

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6 1 **SUPPLEMENTARY ANNEX**

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10 3 **5 QUESTIONS TARGETED FOR THEW SCREENING OF EPILEPSY CASES**  
11  
12 4 *If at least one of the 5 questions is answered with YES, the person will be invited to participate in*  
13  
14 5 *the neurological examination for case verification.*  
15  
16 6

17  
18 7 **QUESTION 1**

19  
20 8 Have you ever lost consciousness and experienced:

21  
22 9 a) Loss of bladder control?  YES  NO  DON'T KNOW

23  
24 10 b) Foam at the mouth?  YES  NO  DON'T KNOW  
25  
26 11

27  
28 12 **QUESTION 2**

29  
30 13 Have you ever experienced absence(s) or sudden loss(es) of contact with the surroundings, for a  
31  
32 14 short duration of time?  YES  NO  DON'T KNOW  
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34 15

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36 16 **QUESTION 3**

37  
38 17 Have you ever experienced sudden, uncontrollable twitching or shaking of your arms, legs or  
39  
40 18 head, for a period of a few minutes?  YES  NO  DON'T KNOW  
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43  
44 20 **QUESTION 4**

45  
46 21 Do you sometimes experience sudden and brief bodily sensations, see or hear things that are not  
47  
48 22 there, or smell strange odours?  YES  NO  DON'T KNOW  
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50 23

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52 24 **QUESTION 5**

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54 25 Have you ever been told that you are suffering from epilepsy or that you have already had  
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56 26 epileptic fits?  YES  NO  DON'T KNOW  
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# BMJ Open

## Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for onchocerciasis, and the potential impact of community-directed treatment with ivermectin: a cross sectional study and comparison over 28 years

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Manuscripts

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3 1 **Evolution of epilepsy prevalence and incidence in a Tanzanian area endemic for**  
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5 2 **onchocerciasis, and the potential impact of community-directed treatment with**  
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7 3 **ivermectin: a cross sectional study and comparison over 28 years**  
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11 5 Helena Greter<sup>a\*</sup>, Bruno Mbando<sup>b</sup>, Williams Makunde<sup>b</sup>, Mohamed Mnacho<sup>c</sup>, William Matuja<sup>c</sup>,  
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## 17 **ABSTRACT**

### 18 **Introduction**

19 Worldwide, there are an estimated 50 million people affected by epilepsy. Its etiology is manifold,  
20 and parasitic infections play an important role, specifically onchocerciasis. In onchocerciasis  
21 endemic areas, a distinctive form of epilepsy has been described as nodding syndrome, affecting  
22 children and causing nodding seizures, mental retardation and debilitating physical development.  
23 Onchocerciasis control programs using community directed treatment with ivermectin (CDTI) are  
24 implemented in endemic countries. This study is designed to contribute to a better understanding  
25 of the linkage between the onset of epilepsy, onchocerciasis and CDTI. Comparing the  
26 epidemiological data on epilepsy and onchocerciasis from pre-CDTI and 20 years after its  
27 introduction will allow identifying a potential impact of ivermectin on the onset of epilepsy.

### 28 **Methods and analysis**

29 The study will be conducted in the Mahenge highlands in Tanzania. Study site selection is based  
30 on an in-depth study on epilepsy in that area dating from 1989. CDTI was introduced in 1997. By  
31 a door-to-door approach, the population will be screened for epilepsy using a validated  
32 questionnaire. Suspected cases will be invited for a neurological examination for case  
33 verification. Onchocerciasis prevalence will be assessed by a rapid epidemiological assessment.  
34 As an indicator for ongoing transmission, children younger than 10 years of age will be tested for  
35 Ov16 antibodies. Ivermectin use will be assessed at household level. Epilepsy data will be  
36 analysed in comparison to the 1989 data to reveal pre- and post-CDTI prevalence and incidence.

### 37 **Ethics and dissemination**

38 The protocol has received ethical approval from the ethics committees of the University of  
39 Antwerp, Belgium and of the National Institut of Medical Research (NIMR), Dar es Salaam,  
40 Tanzania. The findings will be published in peer-reviewed journals, and presented to the health  
41 authorities in Tanzania, at national, regional and village level.

42

### 43 **Strengths and limitations of this study:**

- 44 • This study will allow comparison of large scale population based data on epilepsy  
45 epidemiology in Mahenge over a period of 28 years.
- 46 • The strength of the study is that it is a first study to follow-up epilepsy epidemiology in the  
47 Mahenge area since the introduction of community directed treatment with ivermectin.
- 48 • The comparison of the data obtained in 1989 and 2017 will be challenged by the slightly  
49 different study methodologies used.
- 50 • The study design is limited in accounting for potential confounding factors other than CDTI  
51 that may influence epilepsy incidence and prevalence.
- 52 • Focusing on villages with high epilepsy burden in the past may lead to an overestimation of  
53 the potential impact of CDTI.

### 55 **Key words**

56 Epilepsy  
57 Nodding disease  
58 Onchocerciasis  
59 Ivermectin  
60 Tanzania

## 62 **INTRODUCTION**

### 63 **Epilepsy in onchocerciasis endemic regions in Africa**

64 Epilepsy is a chronic disease estimated to affect 50 million people worldwide according to World  
65 Health Organisation (WHO).<sup>1</sup> In general, higher prevalence and incidence are reported among  
66 those populations living in low and middle income countries (LMICs) when compared to  
67 industrialized countries.<sup>2 3</sup> In fact, more than 85% of the global burden of epilepsy occurs in  
68 people living in LMICs.<sup>4 5</sup> The etiology of epilepsy is very diverse and not yet fully understood.

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3 69 Besides birth trauma and head injury involving the brain, infectious diseases can trigger epilepsy  
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5 70 as well. Several parasitic infections are associated with epilepsy such as cerebral malaria,  
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7 71 neurocysticercosis, echinococcosis, and onchocerciasis.<sup>6-8</sup> Many of these epilepsy cases could  
8  
9 72 be prevented through timely anti-parasitic treatment. Epilepsy manifests in a variety of seizure  
10  
11 73 types and intensity.<sup>9</sup> In the 1960 in Tanzania, Aall-Jillek was the first to describe an unusual form  
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13 74 of epileptic seizures characterized by nodding movements of the head.<sup>10 11</sup> Later, this distinct  
14  
15 75 form of epilepsy has been described also in Uganda and South Sudan, and has been named as  
16  
17 76 nodding syndrome (NS).<sup>12 13</sup> NS is a debilitating epileptic disorder mainly affecting children at the  
18  
19 77 ages of 3 and 18 years.<sup>14</sup> The seizures are characterized by a brief loss of muscle-tone in the  
20  
21 78 neck, leading to repetitive head-nodding.<sup>15</sup> NS is often associated with cognitive decline, and  
22  
23 79 sometimes with stunted growth.<sup>16</sup> So far, NS is solely described in onchocerciasis endemic  
24  
25 80 areas.<sup>12</sup> A NS epidemic has been observed in the past two decades in northern Uganda and in  
26  
27 81 neighboring South Sudan.<sup>17 16</sup> The weight of the public health burden caused by epilepsy in  
28  
29 82 onchocerciasis endemic regions can be illustrated by the situation in the village Mvolo (West  
30  
31 83 Equatorial State in South Sudan) over 50% of the families had at least one child with epilepsy,  
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33 84 resulting in one in six children of the village suffering from epilepsy.<sup>18</sup>  
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35  
36 85 Health systems services in remote rural regions in Africa are rarely capable to provide continuous  
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38 86 anti-epileptic treatment to those patients in need.<sup>5</sup> Further more, most health care workers lack  
39  
40 87 training to diagnose and treat persons with epilepsy adequately. In addition to its clinical burden,  
41  
42 88 epilepsy is perceived as a possession by evil spirits in many African societies and hence bears a  
43  
44 89 stigma that puts the diseased individual and his family at risk for social isolation.<sup>19</sup> Moreover, the  
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46 90 family's economy is negatively impacted by the disease, since an epileptic family member needs  
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48 91 specific care and supervision, detaining care takers from their subsistence duties.<sup>20</sup>  
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51 92 NS only occurs in onchocerciasis endemic areas. An epidemiological association between  
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53 93 epilepsy and onchocerciasis was first reported from western Uganda in the early 1990s.<sup>21 22</sup> A  
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55 94 case-control study performed in 1991-92 in the Mbam valley in Cameroon demonstrated a

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3 95 significantly higher microfilarial load in persons with epilepsy than in controls.<sup>23</sup> Study results from  
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5 96 other onchocerciasis-endemic African countries underline this association.<sup>8 24</sup> To describe this  
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7 97 epidemiological phenomenon the term onchocerciasis associated epilepsy (OAE) was proposed  
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9 98 by Kaiser and colleagues.<sup>24</sup> Case-control studies in northern Uganda and South Sudan focusing  
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11 99 on NS patients produced similar results, showing a higher prevalence of onchocerciasis in NS  
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13 100 cases compared to non-epileptic controls.<sup>16 17</sup> It is, however, unclear how onchocerciasis might  
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15 101 cause NS. Although the eye and the optical nerve are affected when onchocerciasis causes  
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17 102 blindness, microfilariae and adult *Onchocerca volvulus* worms are not generally considered to be  
18  
19 103 able to invade the central nervous system. Recent research hypothesises that an immunological  
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21 104 cross-reaction of onchocerciasis-specific antibodies may provoke a neurotoxic reaction and  
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23 105 trigger NS.<sup>25</sup>

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28 107 **Onchocerciasis, a treatable neglected tropical disease facing obstacles on the road to**  
29  
30 108 **elimination**

31  
32 109 Onchocerciasis is a parasitic disease caused by an infection with the worm *O. volvulus* whose  
33  
34 110 filarial larvae are transmitted by blackflies (*Simulidae* spp.). In the final host (humans) the adult  
35  
36 111 female worms encapsulate in the subcutaneous tissue forming visually detectable nodules. Each  
37  
38 112 female worm releases up to one thousand microfilariae per day. These microfilariae provoke  
39  
40 113 itching, dermatitis and – if left untreated – blindness, leading to the disease name river blindness.  
41  
42 114 Blackflies get infected with microfilariae when biting infected humans in proximity to fast flowing  
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44 115 rivers, the breeding site of the blackflies. After passing through several larval stages, infected  
45  
46 116 blackflies disseminate the parasite by biting other people. Onchocerciasis is treatable with  
47  
48 117 ivermectin.<sup>26</sup> The drug has a twofold mechanism of action: (i) it kills the microfilariae and (ii)  
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50 118 inhibits their release by the adult female worm for several months up to two years after a single  
51  
52 119 dose treatment.<sup>27</sup> Hence, ivermectin has a strong impact on reducing transmission. However,  
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54 120 ivermectin is not lethal to adult worms and infected persons have to be treated annually for up to  
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3 121 15 years.<sup>28</sup> Onchocerciasis is a priority disease scheduled for elimination by 2025 by the WHO.  
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5 122 Today, 99% of the globally 37 million people infested live in Africa.<sup>1</sup> In 1995, the African Program  
6  
7 123 for Onchocerciasis Control (APOC) was initiated for the implementation of the onchocerciasis  
8  
9 124 control programme based on community directed treatment with ivermectin (CDTI). APOC was  
10  
11 125 coordinating these activities in endemic areas of 22 African countries.<sup>29</sup> Since May 2016, CDTI  
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13 126 control programmes are integrated in the WHO Expanded Special Project for Elimination of  
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15 127 Neglected Tropical Diseases (ESPEN).<sup>30</sup> CDTI overcomes the limited performance of weak  
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17 128 health systems in rural areas by using an active strategic involvement of the community.<sup>31</sup> To  
18  
19 129 reach the entire population, ivermectin distribution is organized by trained volunteers in each  
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21 130 village, resulting in a large geographical coverage. CDTI, in certain regions combined with the  
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23 131 control of the blackfly by larviciding of breeding sites (i.e. fast flowing rivers), resulted in a  
24  
25 132 measurable impact reflected by a remarkable transmission reduction in the past 20 years.<sup>32</sup> But  
26  
27 133 success and effectiveness of these targeted interventions lack comprehensiveness. Certain  
28  
29 134 onchocerciasis endemic regions remain undersupplied or unreachable for CDTI due to political  
30  
31 135 instability, insecurity or armed conflicts.<sup>33</sup> As a consequence in the war-affected regions of South  
32  
33 136 Sudan and northern Uganda, onchocerciasis control measures were stopped or implementation  
34  
35 137 started only recently. Moreover, misconceptions and the fear of adverse effects result in  
36  
37 138 suboptimal therapeutic coverage and reduce the effectiveness of the control program.<sup>34</sup> Adding  
38  
39 139 to the complexity of onchocerciasis control, in regions where *Loa loa* and onchocerciasis are co-  
40  
41 140 endemic, ivermectin may cause severe adverse effects (encephalopathy, coma or death) in  
42  
43 141 infected individuals harbouring a high *Loa loa* microfilariae load.<sup>35 36</sup> Thus, CDTI implementation  
44  
45 142 in such regions requires additional precautions.<sup>37</sup> This is the case in certain regions of Cameroon  
46  
47 143 and the Democratic Republic of Congo (DRC).<sup>38</sup> Compliance to CDTI programs can also  
48  
49 144 decrease over the years since less direct positive effects can be observed when onchocerciasis  
50  
51 145 prevalence drops, and healthy feeling people may not appreciate the importance of continuing  
52  
53 146 repeated treatment.<sup>39</sup>



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3 173 The population based study from 1989 by Rwiza et al. established the baseline prevalence of all  
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5 174 forms of epilepsy in the Ulanga district, Tanzania.<sup>43</sup> This population-based study aims to further  
6  
7 175 evaluate the prevalence and incidence rates of new epilepsy cases, including a complete case  
8  
9 176 ascertainment of all forms of epilepsy encountered, and compare the data to the 1989 data  
10  
11 177 (Table 1).

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15 179 **Table 1. The pre- and post-CDTI epilepsy study periods and estimated epilepsy prevalence**  
16  
17 **and incidence in the Mahenge area, Ulanga district in Tanzania.**  
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19

Mahenge area, Ulanga district, Tanzania		
Year of epilepsy study data collection	1989 <sup>43</sup>	2017
Status of CDTI at study year	Pre-CDTI	Post-CDTI (ongoing since 1997)
Estimated epilepsy prevalence	20.2/1'000	14/1'000*
Estimated epilepsy incidence	146/100'000	81.7/100'000**

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32 181 \*Median epilepsy prevalence and \*\*incidence in low and middle income countries<sup>4 3</sup>  
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34 182  
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36 183 **Objective**  
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38 184 The main objective of this study is to identify the potential impact of long-term onchocerciasis  
39  
40 185 control using CDTI on the prevalence and incidence of epilepsy in selected villages in the  
41  
42 186 Mahenge area of the Ulanga district in Tanzania.  
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45 187  
46  
47 188 **Specific objectives**  
48  
49 189 1. To determine the prevalence of all forms of epilepsy in selected villages of the Mahenge area  
50  
51 190 and compare the related data from 2017 to the 1989 data.  
52  
53 191 2. To determine the incidence rate of annual new onset cases of all forms of epilepsy in the  
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55 192 Mahenge area and compare the related data from 2017 to the 1989 data.  
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3 193 3. To assess the ivermectin coverage and the onchocerciasis prevalence with a REMO  
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5 194 assessment in selected villages of the Mahenge area.

7 195 4. To determine the level of onchocerciasis transmission by a serological survey using a rapid  
8  
9 196 test among children in selected villages of the Mahenge area.

11 197 5. To investigate the potential difference in clinical appearance of epilepsy in patients with  
12  
13 198 negative onchocerciasis serology to patients with positive onchocerciasis serology.

15  
16 199

## 18 200 **METHODS AND ANALYSIS**

19  
20 201 The study consists of two parts: (I) a study to determine the prevalence and incidence of epilepsy  
21  
22 202 and (II) a study to determine ivermectin coverage, onchocerciasis prevalence and level of  
23  
24 203 transmission. Data collection was carried out between January and September 2017. Analysis is  
25  
26 204 planned to be finalized by end of 2017, to allow publishing of the results in 2018.

### 28 205 **Study site**

29  
30 206 The study is taking place in the Mahenge area of the Ulanga district, Morogoro region in south-  
31  
32 207 eastern Tanzania, a mountainous area with fast flowing rivers.

### 34 208 **Epilepsy in the Mahenge area**

35  
36 209 In the 1960s, Aall-Jilnek was the first to report a high burden of epilepsy in the Mahenge area,  
37  
38 210 and also described the first NS cases.<sup>10</sup> In 1989, Rwiza et al. carried out a population based  
39  
40 211 survey to determine prevalence and incidence of epilepsy in the Ulanga district and found an  
41  
42 212 annual incidence of 73.3 new cases in 100'000. The prevalence was 10.2 cases in 1000, and  
43  
44 213 varied between villages from 5.1 to 37.1 cases in 1'000. Those villages with the highest  
45  
46 214 prevalence were located in the Mahenge highlands (Table 2).<sup>43</sup>

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216 **Table 2. Population size and prevalence of epilepsy in some villages of the Ulanga district,**  
 217 **Tanzania, showing the highest prevalence in 1989, as reported by Rwiza et al. in 1992**

Name of Village	Population size	Number of Epilepsy cases	Prevalence per 1000 people
Sali <sup>δ</sup>	1'282	14	10.9
Mdindo <sup>δ</sup>	539	20	37.1
Vigoi <sup>δ</sup>	1'822	23	12.6
Lupiro	1'697	17	10
Misegezi	1'667	18	10.8
<b>Total</b>	<b>7'007</b>	<b>92</b>	<b>13.13</b>

218 <sup>δ</sup>Located in Mahenge highlands

219

## 220 **Onchocerciasis and CDTI in the Mahenge area**

221 The Morogoro region is among the five regions where onchocerciasis is endemic in Tanzania. The  
 222 region presents four foci: Uluguru mountain, Ulanga/Mahenge, Kilosa and the Nguru mountain  
 223 foci.<sup>44</sup> The Ulanga district, specifically the Mahenge area, was known for its high endemicity of  
 224 onchocerciasis since the early last century.<sup>45</sup> Mass drug administration using annual CDTI was  
 225 introduced in the Mahenge area in 1997.<sup>46</sup> Before CDTI was implemented, 58.6% of the 482  
 226 inhabitants of the Mahenge area tested were found to have a microfilariae positive skin snip.<sup>47</sup>  
 227 Twelve years later (in 2009) the rapid epidemiological mapping of onchocerciasis (REMO) in 10  
 228 villages in the Mahenge area revealed that the percentage of persons with a microfilariae positive  
 229 skin snip has dropped to 21.9%, with a mean prevalence of 8.3%.<sup>32</sup>

## 230 **Study population**

231 The three villages Mdindo, Vigoi and Misegezi that had high epilepsy prevalence during the 1989  
 232 study will be selected for this study.<sup>43</sup> The entire population of each of these villages will be  
 233 included in the study.

234

## 235 **Epilepsy and NS prevalence / incidence study**

### 236 **Study design**

237 The study is designed as a population-based cross-sectional study, following a two-stage  
238 approach for epilepsy case identification at village level. The gold-standard in neuro-  
239 epidemiological surveys to identify epilepsy cases in LMICs, the door-to-door approach, will be  
240 applied.<sup>48</sup> All inhabitants of the selected villages will be eligible for participation and will be  
241 included in the questionnaire screening survey. Due to well described limitations of questionnaire  
242 studies on epilepsy (stigma leading to concealment of cases, recall bias, absence of clear  
243 terminology for epilepsy and seizures) and to increase sensitivity of case ascertainment, key  
244 informants who are likely to be aware of persons with epilepsy in the village will additionally be  
245 consulted.<sup>3 48</sup> These may be health workers, traditional healers, teachers, or community  
246 leaders.<sup>49</sup>

247 In a second stage, persons with suspected epilepsy identified during the household screening  
248 survey will be further invited for clinical examination by a neurologist. The examination will  
249 include neurological tests and a detailed interview for case verification. In verified epilepsy cases  
250 the onset of the seizures will be determined and possible etiologic factors will be investigated,  
251 such as birth trauma, head injury, meningo-encephalitis, cerebral malaria, neurocystocercosis,  
252 and the history of onchocerciasis. For persons with suspected epilepsy their serological status  
253 will be determined using onchocerciasis rapid diagnostic test (Ov16 RDT) (Standard diagnostics,  
254 Inc., Gyeonggi-do, Republic of Korea).

### 255 **Sample size calculation**

256 According to Rwiza et al. (1992) the average prevalence of epilepsy in five villages with high  
257 prevalence was 1.313% (Table 2). If we assume a reduction in the prevalence by 33.3% to be  
258 able to compare the prevalence at a power of 80% and 95% confidence level, the minimal  
259 sample size of 4,746 individuals will be required. Assuming a participation of 80%, a minimum  
260 source population of 5,933 is necessary to obtain optimal sample size.  
261 Since 1989 the population in the villages with high epilepsy prevalence has increased (Table 3).

262 For this survey we will include only the population of the villages with the highest epilepsy  
 263 prevalence in 1989. The total population of the selected villages of Mdingo, Vigoi and Mizegezi in  
 264 2016 is about 7,766.

265

266 **Table 3. List of the study villages in the Mahenge highlands, Tanzania, and their**  
 267 **population size in 1989 and in 2016.**

Name of Village	Population size (1989)	Population size (2016)
Mdingo	539	1'536
Vigoi	1'822	2'572
Mizegezi	1'667	3'658*
<b>Total</b>	<b>4'028</b>	<b>7'766</b>

\*Population projection based on the growth rate of Vigoi village

268

### 269 Data collection at community level

270 The community survey will commence by a questionnaire interview with the village authorities on  
 271 demographic topics, and with village health workers to address general questions on the status  
 272 of epilepsy and epilepsy treatment in the village. A complete door-to-door active screening for  
 273 persons with suspected epilepsy at village level will be performed. The interview team will be  
 274 trained on how to conduct the active search for epilepsy cases using a pre-tested, validated  
 275 screening questionnaire targeting epilepsy by 5 specific questions (provided in the  
 276 supplementary material).<sup>50 51</sup> For validation, the questionnaire will be translated to Kiswahili,  
 277 pretested and retranslated to English. The locally used terms for the two respective conditions  
 278 will be used (epilepsy: *kifafa*, NS: *kusinzia kichwa*). To ascertain completeness and to ensure the  
 279 best collaboration with the village population, the interviewer team will be accompanied to all  
 280 households by local village health workers. The geographical coordinates of the participating  
 281 households will be collected for the mapping and geospatial analysis of cases (proximity to rivers,  
 282 potential clustering).

### 283 **Case verification and validation**

284 All persons with suspected epilepsy identified during the door-to-door survey will be verified by a  
285 neurologist. The neurologist will perform a detailed anamnesis on all persons with suspected NS  
286 and epilepsy. In case of confirmation of the epilepsy, the neurologist will perform a medical  
287 examination and administer a detailed questionnaire on the type of epilepsy. Newly diagnosed  
288 epilepsy cases will be referred to an epilepsy treatment centre. In case the person is already  
289 followed in a treatment centre, permission will be asked to review the medical information  
290 available in the treatment centre to record epilepsy diagnosis and epilepsy treatment history.

#### 291 **Definitions:**

- 292 - A case of epilepsy will be defined as a patient who had at least two times nonfebrile  
293 seizures unrelated to any acute metabolic disorder or to withdrawal of alcohol or drugs,  
294 with a minimal time difference of 24h between the two events. This is in accordance to the  
295 current guidelines of the International League Against Epilepsy (ILAE) for an operational  
296 definition of epilepsy and to the definition used by Rwiza et al in their baseline study  
297 performed in 1989.<sup>43 49 52</sup>
- 298 - A case will be considered as active epilepsy if the patient is receiving epilepsy treatment  
299 or, if without anti-epileptic treatment, the patient presented at least one seizure during the  
300 last 5 years.
- 301 - A case of suspected NS will be defined as a person who presented with episodes of  
302 decreased consciousness during which the head dropped forward repeatedly.
- 303 - New cases of epilepsy will be defined as cases that appeared within the last 12 month  
304 preceeding the study period.

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306

### 307 **Onchocerciasis prevalence study**

#### 308 **Study design**

1  
2  
3 309 This study includes two approaches. The aim of the first approach will be to determine the  
4  
5 310 onchocerciasis prevalence in the selected villages after 20 years of CDTI by performing the WHO  
6  
7 311 proposed REMO methodology.<sup>53</sup> In brief, in each study village, 50 adults aged at least 20 years  
8  
9 312 old and resident in the community for at least 10 years will be invited to participate. They will be  
10  
11 313 examined for the presence of onchocerciasis nodules (subcutaneous nodules or deep, painless,  
12  
13 314 firm, mobile nodules located over bony prominences: pelvic girdle, costal grid, knees, and skull).  
14  
15 315 Although pre-control onchocerciasis prevalence data from the study villages is not available, a  
16  
17 316 study from 1966 carried out in three villages in Mahenge found a skin snip positivity rate ranging  
18  
19 317 from 43to 65%.<sup>54</sup>  
20  
21  
22 318 The second approach aims at determining the level of transmission of onchocerciasis in the  
23  
24 319 selected villages. Therefore, serological testing for onchocerciasis will be done in all children  
25  
26 320 aged 7-10 years old, using the onchocerciasis specific Ov16 RDT (Standard diagnostics, Inc.,  
27  
28 321 Gyeonggi-do, Republic of Korea). According to the National Census survey in 2012, the  
29  
30 322 population of children aged 7-10 years represented 11.6% of the population in Ulanga district.  
31  
32 323 Estimated population of children aged 7-10 years from the four selected villages is 900 of which  
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34 324 722 (~80%) are anticipated to participate in the survey giving a power of 85% in detecting the  
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36 325 prevalence between 0.8 to 2% at 5% significance level (Table 4).  
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39 326  
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41 327 **Table 4. Estimated number of children aged 7 to 10 years old in the study villages in the**  
42  
43 328 **Ulanga district, Tanzania, in 2016.**

<b>Name of Village</b>	<b>Population size (2016)</b>	<b>Estimated Population aged 7-10 yrs</b>	<b>Estimation of participating children (80%)</b>
Mdindo	1'536	178	143
Vigoi	2'572	298	239
Misegezi	3'658*	424*	340*
<b>Total</b>	<b>7'766</b>	<b>900</b>	<b>722</b>

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*\*Population projection based on the growth rate of Vigoi village*

329

### 330 **Data collection procedures**

331 Data collection will be done using numeric tablets. All data collection forms will be developed in  
332 the open source software 'Open Data Kit' (ODK, <https://opendatakit.org/>). Interviewers will be  
333 trained in how to perform tablet-based surveys. A technical data coordinator will be assigned to  
334 guarantee completeness and quality of data, and to assure daily data transfer from each tablet to  
335 the central server for data security.

### 336 **Data management and analysis**

337 The prevalence of epilepsy and NS will be computed as a ratio of the number of epilepsy and NS  
338 cases per total number of people registered in the households visited, respectively. The  
339 incidence of new cases of epilepsy is defined as the number of persons who developed epileptic  
340 seizures within two years preceding the study, divided by twice the population size, assuming  
341 that the change in population within the two years has a minimal effect on the incidence. Results  
342 will be presented accompanied with 95% confidence interval (95%CI), and P-value<0.05 level of  
343 significance. Prevalence and incidence will be compared between villages and to the 1989 data.  
344 Ivermectin treatment coverage and onchocerciasis prevalence will be calculated. Proportions will  
345 be compared using  $\chi^2$ -test, while means will be compared using t-tests. Demographic and clinical  
346 characteristics of persons with epilepsy having a positive Ov16 serology will be compared to  
347 epilepsy cases with negative Ov16 serology. Ivermectin treatment coverage, epilepsy prevalence  
348 and incidence and OV16 positivity rate among children aged 7-10 years old will be compared  
349 among villages, weighted for the difference in population size between villages. Odds ratios will  
350 be calculated for epilepsy cases with positive Ov16 results, and the association of Ov16 positivity  
351 and epilepsy will be analysed by age group.

352

### 353 **Ethics**

1  
2  
3 354 The protocol has received ethical approval from the ethics committee of the University of  
4  
5 355 Antwerp, Antwerp, Belgium (29.08.2016) and the National Institute of Medical Research (NIMR)  
6  
7 356 ethical committee Dar es Salaam, Tanzania (24.08.2016). Before the activities start, the research  
8  
9 357 team will hold meetings with community leaders and health workers of the selected villages. The  
10  
11 358 procedure, purpose and specific aim of the study will be explained and discussed with regard to  
12  
13 359 the potential risks and benefits for the community. Community leaders, village health workers and  
14  
15 360 researchers will maintain the initially established communication for the entire duration of the  
16  
17 361 study. The dissemination of results will be organized in a similar way as the initial meeting.  
18  
19 362 As approved by the relevant ethics committees, only participants who provide written informed  
20  
21 363 consent will be enrolled in the study. Participant information sheets and consent forms will be  
22  
23 364 available in English and Kiswahili. In case of illiteracy, information sheets and consent forms will  
24  
25 365 be read to the participant in the presence of a witness. All participants will be permitted to  
26  
27 366 withdraw from the study activities, without reason, at any time. All personal information, samples  
28  
29 367 and test results will be encoded and treated confidentially. People identified with untreated  
30  
31 368 epilepsy or with interrupted treatment will be referred to the treatment centre and will receive  
32  
33 369 advice for care and support.  
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35

### 36 **Data storage and handling**

37  
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39 371 All data files will be centralised and stored in a secured central server. Name-linked information  
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41 372 on participants and ID codes will remain confidential and will be used only to communicate  
42  
43 373 clinical results to participants for their respective treatments.  
44

45 374

## 46 **DISCUSSION**

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48  
49 376 The central research question of this study is to determine whether mass ivermectin  
50  
51 377 administration using CDTI has the potential to prevent the onset of OAE. The expected results  
52  
53 378 will contribute to a better understanding of the linkage between the onset of epilepsy and NS in  
54  
55 379 particular, onchocerciasis and the impact of CDTI. In northern Uganda, an NS epidemic has been  
56  
57



1  
2  
3 380 halted after introducing a programme combining CDTI and larviciding of the main rivers. This  
4  
5 381 study will be the first to investigate systematically whether CDTI alone may reduce epilepsy in an  
6  
7 382 onchocerciasis endemic region. To do so pre- and post-CDTI epilepsy prevalence and incidence  
8  
9 383 data will be compared. Concurrently, with the Ov16 serological survey among children aged 7-10  
10  
11 384 years, it will be possible to assess whether the transmission of onchocerciasis is ongoing in the  
12  
13 385 Mahenge area after 20 years of CDTI. So far, the onchocerciasis control program in the study  
14  
15 386 area was monitored based on annual ivermectin distribution, treatment coverage data being  
16  
17 387 provided by the community distributors. Also, ivermectin treatment coverage data will be  
18  
19 388 assessed in the framework of this study by interviewing the population. Moreover, by performing  
20  
21 389 an Ov16 seroprevalence study among children under 10 years of age, a real-time estimate of the  
22  
23 390 level of ongoing transmission of onchocerciasis will be evaluated. The hypothesis is to find a low  
24  
25 391 Ov16 seroprevalence in children and a decreased prevalence of epilepsy since 1989. In case a  
26  
27 392 high Ov16 seroprevalence is found, this will suggest that the CDTI programme was performing  
28  
29 393 suboptimal and/or that ivermectin resistance may have developed. It might therefore be useful to  
30  
31 394 combine CDTI with larviciding rivers to reduce blackfly abundance.

32  
33  
34 395 This study also has limitations. The methods used will not allow for measuring onchocerciasis  
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36 396 infection intensity, one of the main factors influencing the development of OAE. There is a  
37  
38 397 possibility that it may not be possible to show an impact of CDTI because in case of high level  
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40 398 exposure to infectious blackflies the administration of ivermectin only once a year may not be  
41  
42 399 sufficient to considerably decrease onchocerciasis transmission. Moreover, in pre- and post-  
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44 400 CDTI comparison it is possible that observed differences in epilepsy prevalence and incidence  
45  
46 401 are not related to the intervention (CDTI) but to some of the other factors (e.g. those mentioned  
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48 402 in Fig. 1) that might have changed over time. However, a site visit to the Mahenge study site  
49  
50 403 revealed that the village population had increased by a factor of 3, but there was no important in-  
51  
52 404 or out migration or any other major change in lifestyle of the population or another major  
53  
54 405 environmental change. In all the villages included in the study, such potential changes will be



1  
2  
3 406 carefully assessed to control for potential confounding factors. Families who migrated into the  
4  
5 407 study area after the implementation of CDTI will not be included in the analyses.  
6

## 7 408 **Outlook**

9 409 This study aims to unravel the potential impact of CDTI on reducing the incidence of epilepsy in  
10  
11 410 onchocerciasis endemic areas. Study results may provide evidence that strengthening CDTI  
12  
13 411 programs could prevent the onset of OAE. The results and lessons learned from this study will be  
14  
15 412 disseminated by publications in open access journals, as well as presentations at scientific  
16  
17 413 conferences and shared with all interested health authorities in Tanzania and beyond.  
18  
19

20 414

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22  
23  
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25  
26 417 Tanzania, and the health authorities in Vigoi, Mbindo and Misegezi for the fruitful discussions  
27  
28 418 during our visit and for their input that provided background information and practical  
29  
30 419 considerations for the development of the current study protocol.  
31

32 420

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12 585 **Authors' contribution**

13  
14 586 All listed authors contributed to the development of the study design, essential study documents  
15  
16 587 and study tools. According to their different areas of expertise, the authors critically revised  
17  
18 588 specific parts of this manuscript: HG wrote the manuscript; HG, BM, PS, RC developed the study  
19  
20 589 protocol; WM, MM, WM developed and approved the neurological study protocol and the survey  
21  
22 590 tools; HG, BM, AK, developed the methodology and tools for the digital data collection; HG, BM,  
23  
24 591 RC visited the study sites.  
25

26  
27 592 **Data sharing statement**

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29 593 Data will be available from the Global Health Institute of the University of Antwerp at  
30  
31 594 [https://pintra.uantwerpen.be/webapps/cmsmain/webui/\\_xy-914103\\_1-t\\_KW7pxaf1](https://pintra.uantwerpen.be/webapps/cmsmain/webui/_xy-914103_1-t_KW7pxaf1)  
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41  
42 599 **Competing interests**

43  
44 600 The authors declare that they have no competing interests.  
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53 604 **Figure caption**  
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3 605 **Figure 1.** Onchocerciasis endemicity and prevalence and incidence of associated epilepsy are  
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5 606 influenced by an extensive network of controllable and uncontrollable factors.  
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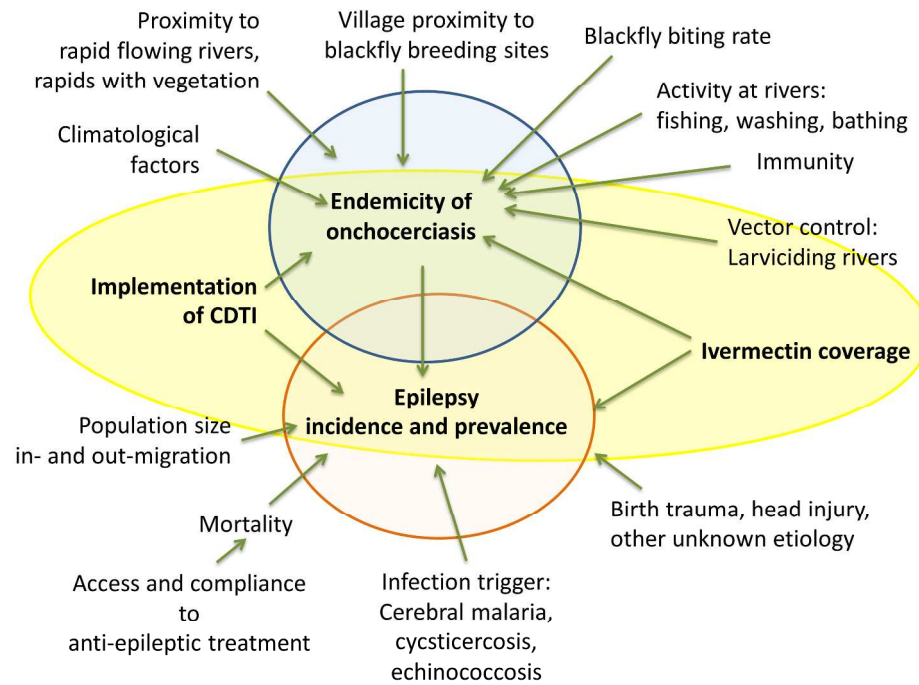


Figure 1. Onchocerciasis endemicity and prevalence and incidence of associated epilepsy are influenced by an extensive network of controllable and uncontrollable factors.

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6 **1 SUPPLEMENTARY ANNEX**

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10 **3 5 QUESTIONS TARGETED FOR THEW SCREENING OF EPILEPSY CASES**

11  
12 *If at least one of the 5 questions is answered with YES, the person will be invited to participate in*  
13  
14 *the neurological examination for case verification.*

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18 **7 QUESTION 1**

19  
20  
21 Have you ever lost consciousness and experienced:

22  
23 a) Loss of bladder control?  YES  NO  DON'T KNOW

24  
25 b) Foam at the mouth?  YES  NO  DON'T KNOW

26  
27  
28 **12 QUESTION 2**

29  
30 Have you ever experienced absence(s) or sudden loss(es) of contact with the surroundings, for a  
31  
32 short duration of time?  YES  NO  DON'T KNOW

33  
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35  
36 **16 QUESTION 3**

37  
38 Have you ever experienced sudden, uncontrollable twitching or shaking of your arms, legs or  
39  
40 head, for a period of a few minutes?  YES  NO  DON'T KNOW

41  
42  
43  
44 **20 QUESTION 4**

45  
46 Do you sometimes experience sudden and brief bodily sensations, see or hear things that are not  
47  
48 there, or smell strange odours?  YES  NO  DON'T KNOW

49  
50  
51  
52 **24 QUESTION 5**

53  
54 Have you ever been told that you are suffering from epilepsy or that you have already had  
55  
56 epileptic fits?  YES  NO  DON'T KNOW