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ABSTRACT:

Nodding Syndrome (NS) was recently described in children in Northern Uganda. The affected children were in the age group 5 – 15 years. They were stunted, malnourished, dehydrated, mentally retarded and get recurrent seizures. The objective of this study was to describe the cluster distribution of NS cases in Northern Uganda. We conducted a cross-sectional study using available data on the burden of NS in Northern Uganda and used GPS to map the locations of the most affected areas. The results obtained indicate that Nodding Syndrome in Northern Uganda occurs in clusters in the following locations Odek, Atiak, Angagura, Awere, Laguti, Labongo-Amida, Atanga, Pajimo, Palabek Kal and Palabek Gem sub counties and mainly along Aswa and Pager rivers and their tributaries. Nodding Syndrome in Northern Uganda occurs in clusters predominantly along two rivers; perhaps it is an indication for environmental, dietary and common epidemiological exposures for the syndrome.

Keywords: Nodding Syndrome, cluster, Northern Uganda
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INTRODUCTION:

Nodding Syndrome (NS) is an unexplained neurologic illness that has been reported among persons in some sub-Saharan African countries in recent years [1, 2, 3]. In two of the three regions where it has been reported recently, the syndrome has occurred among internally displaced persons or those formerly displaced and later returned to their villages [1-5]. Nodding Syndrome is a clinical constellation of symptoms that most times begin with head nodding and later may result in progressive neurological deterioration [1-5]. Onset is common in children between the ages of 5 and 15 years. The most characteristic feature is a paroxysmal "spell" in which the head bobs forward repeatedly over a period of minutes; in most cases, the child appears unresponsive during the episode [1-5]. The disease has been investigated previously in Southern Sudan in 2001-2003 [3] and Tanzania in 2008 [1].

Ministry of Health in Uganda began investigating a cluster of cases of NS in early 2009 and made several trips to affected district of Kitgum in northern Uganda over the course of the year in an attempt to understand and control the disease [6]. It was estimated by the district health officer that the outbreak in Kitgum district may have affected up to 2000 children [6]. Subsequent investigations resulted in the generation of an extensive list of possible causes for the syndrome including viral, bacterial, parasitic infectious diseases, nutritional deficiencies, and genetic disorders, exposures to heavy metals or pesticides, slow virus or prion diseases, exposures to munitions from the war, post-traumatic stress, mass hysteria, pseudo-seizures and a number of others [6]. Because of the complex nature of the disease and the range of possible aetiologies, the Uganda Ministry of Health requested assistance from the U.S. Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) to conduct a more detailed investigation [6].

The investigative approach was multi-faceted and included a formal review of existing knowledge about the disease, the establishment of a multidisciplinary investigative team, and a phase of hypotheses refinement using qualitative focus groups and key informant interviews [6]. The investigation suggested that NS is a distinctive clinical entity affecting many children in Kitgum, Pader, and Lamwo districts [6]. In addition, NS in these districts share most of the epidemiological and clinical features of previously described "Head Nodding Syndrome" in Southern Sudan and in Tanzania. It was concluded that it was likely that the illnesses occurring in these three

geographic areas (Northern Uganda, Southern Sudan and Tanzania) represented the same clinical entity [6].

Clustering of Nodding Syndrome in Northern Uganda:

There is a clear observation that NS occurs as clusters and mainly along the two major rivers of Pager and Aswa in Northern Uganda; perhaps an indication of environmental contaminations. This cluster occurrence presents both valuable opportunities and methodological problems for the study of epidemiology of this syndrome [7]. Researchers have argued that epidemiological studies could uncover leads to the cause of a particular disease especially those occurring in clusters; it could help evaluate the cause/risk factors of the disease and the possible effect of environmental contaminant which could be important for the assessment of human responses to multiple exposures such as chemicals [7]. This knowledge could in turn help to identify causes/risk factors of NS and could guide policy makers in decision making in the case of environmental contamination as the risk factor [7].

The aim of this epidemiological study was therefore to understand and describe the pattern of occurrence of NS and by inference develop approaches to aid prevention.

The objectives of this study were to use Global Positioning System (GPS) to mark, correlate and map high burden areas of NS in northern Uganda and to compare the data obtained with the CDC findings of 2009; in addition to describe the sites with the heaviest burden of Nodding Syndrome in relations to river network in the region.

MATERIALS AND METHODS:

The study was conducted in Pader, Kitgum, Lamwo, Amuru and Gulu districts in August-September 2012. It was estimated through surveillance records from the offices of the district health offices that over 3000 children in these 5 districts had NS and that over 200 children had died of diseases related to it. Part of these areas under study was part of the areas covered by the CDC study in 2009 [6]. This region is just recovering from over 20 years of civil war. Gulu is one of the regional centers for northern Uganda and draws a largely rural population; many of whom lived in the internally displaced people (IDP) camps for the past 10 to 12 years for safety from the insurgency.

This was a cross sectional study design; GPS was used to map out the sub counties with the highest density of NS.

The study sites were selected based on the number of NS already confirmed and available at the District Health offices. These cases were screened and confirmed as probable cases

using the WHO epidemiological surveillance case definition for Nodding Syndrome [19].

Data collection: GPS locations for sites with high density of probable cases of NS were marked and recorded with the Trimble GeoXT GPS unit. Surveillance data on probable NS included the names of the patients, their villages; parishes and sub counties which were recorded and used to locate the homes of the probable cases. The location was identified and marked on the GPS machine and coordinates stored in a developed shape files and later aggregated and plotted on a map to show the number of cases per Sub County.

Data Analysis: GPS recordings were transferred to a database and plotted on map of the region for easy interpretation and evaluation. The maps including the river network were integrated with the aggregated data of the probable cases of NS per Sub County. The machine was also used to calculate the distances of the cases from the rivers in the region.

RESULTS:

The pattern of distribution of probable cases of NS have remained consistent over the last three years as observed by the studies conducted in CDC in 2009 and another repeated in 2012 by the same authors [6]. As can be observed the first two figures, river Pager appears prominently in this GPS map distribution for both studies of 2009 and 2012.

Figure 1 show the CDC findings of 2009 where samples were collected from probable cases of NS [6]. Probable cases were marked by green dots and suspected cases marked with yellow dots. The areas marked by large circle (red and blue lines) represented those areas in Kitgum and Lamwo districts with the highest burden of NS at the time and most of them were observed to occur along the Pager River.

Figure 2 shows the locations of the current distribution of probable cases of NS in the sub region. The round white in pink circles shows the current distribution of probable cases. The current marking on the map was superimposed on the map used by CDC in 2009 to show and compare whether there were any significant differences in the distribution of NS in the region. These sites were found in Kitgum, Pader, Lamwo, Amuru and Gulu districts. The areas marked by large circle (blue and red) covered those areas with the highest burden of NS in Kitgum, Pader and Lamwo districts and were found mainly along the Pager River and its tributaries (Lanyadyang and Awuc). The areas marked by small-yellow circles indicated sites that were described to have suspected cases in 2009 but were confirmed as probable cases in 2012 by the Ministry of Health.

Figure 1: Map of Kitgum, Lamwo and Pader districts where NS were previously sampled in 2009 by CDC [6]

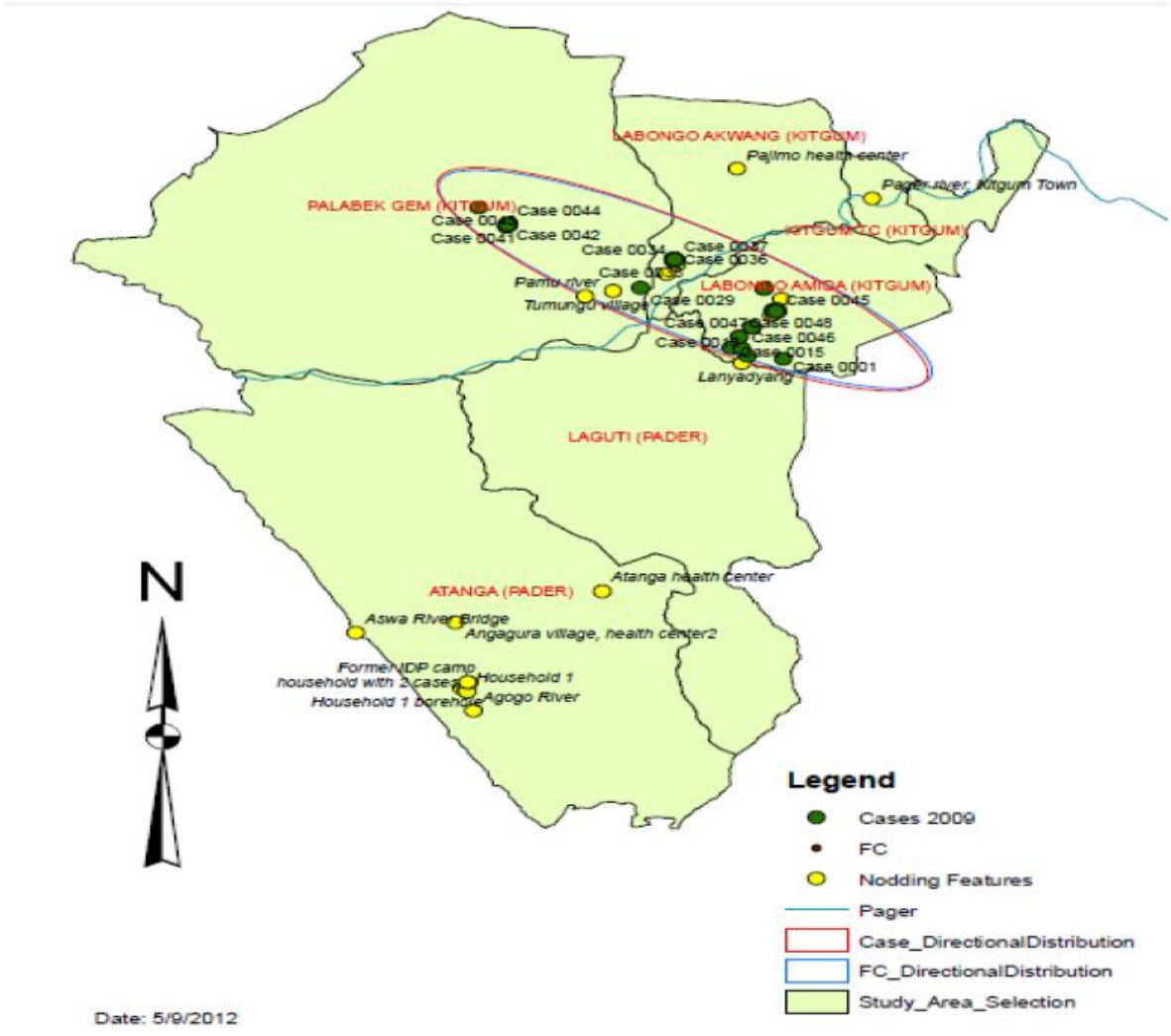

Figure 2: Map of Kitgum, Lamwo and Pader districts were NS were currently confirmed in 2012 [6]

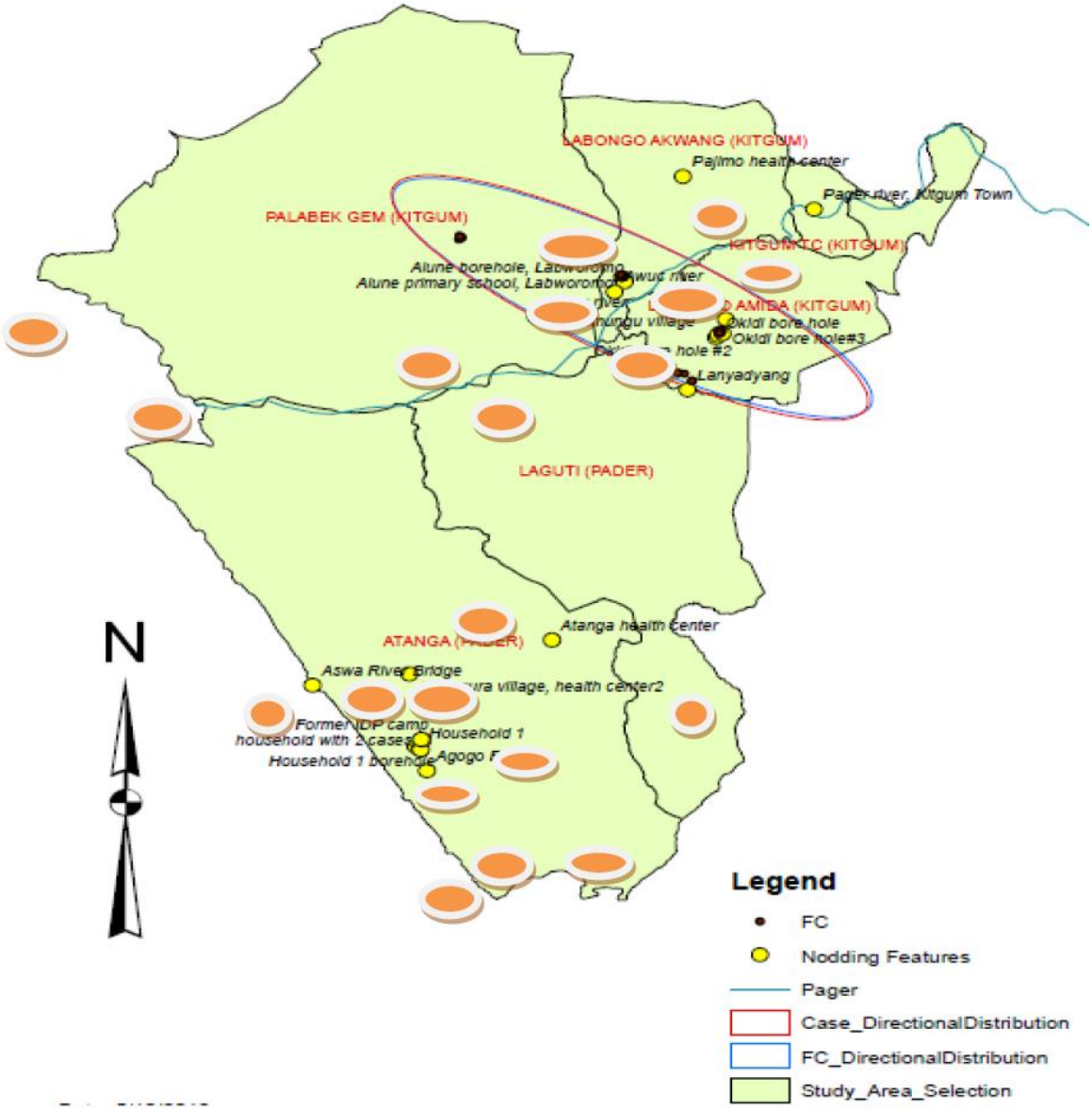

Table 1: Shows the occurrence of Nodding Syndrome in sub counties along specific rivers in Northern Uganda

Gulu District	Sub County	Number of NS cases	River
	Odek	100	Aswa
	Palaro	10	Aswa
	Cwero	15	Aswa
	Paicho	15	Aswa
Amuru District			
	Atiak	80	Unyama/Aswa
Pader District			
	Awere	80	Aswa
	Atanga	314	Ajan
	Laguti	215	Ajan
	Angagura	210	Aswa/Agago
	Acholi bur	30	Lanyadyang
	Puranga	15	Aswa
	Kilak	30	Agago
	Pajule Lapul	64	Agago
	Patongo/Pader	2	Agago
Kitgum District			
	Labongo-Amida	80	Pager/ Lanyadyang
	Labongo-Layamo	40	Pager
	Labongo-Akwang	50	Pager
Lamwo District			
	Palabek Kal	60	Pager/Aswa
	Palabek Gem	120	Pager/ Aswa

(Source of data is from the DHO's office of respective districts)

Table 1 shows the distribution of NS by Sub County in the 5 districts of the Acholi sub-region: Odek, Palaro, Cwero, Paicho sub counties in Gulu district; Atiak in Amuru district; Awere, Atanga, Laguti, Angagura, Acholibur, Pajule-Lapul, Puranga, Kilak, Pader/Patongo in Pader district; Labongo-Amida Labongo-Akwang and Labongo-Layamo in Kitgum district; Palabek Gem and Palabek Kal in Lamwo district. The four sub counties in Gulu districts were situated along Aswa River; Atiak in Amuru district is along Unyama River which is a tributary of Aswa River. Similarly, the 2 sub counties in Lamwo are situated and bordering Pager and Aswa rivers and the sub counties in Kitgum district are traversed by Pager River.

The sub counties in Pader have several tributaries of the 2 main rivers (Pager and Aswa) that traversed it. These tributaries included; Lanyadyang in Acholibur; Ajan in Laguti and Atanga; Agago River in Angagura, Pajule-Lapul and Kilak sub counties.

The Rivers shown in the map above includes Pager which traverses through Kitgum town and later joins Aswa; Agago River which joins Aswa in Pader district. These main rivers (Pager, Agago and Aswa) all originate from Karamoja region (the mountains in Moroto and Kotido districts) [20].

DISCUSSION:

The distribution of Nodding Syndrome in northern Uganda represents a disease clustering in specific geographical locations. The cases mainly occur along the tributaries of the 2 major rivers - Aswa and Pager whose main water supplies originate from the hills and mountains in Karamoja region in north eastern Uganda. These NS clusters are on either side of these 2 rivers and within specific locations of: Odek, Paicho, Palaro and Cwero in Gulu district; Atiak in Amuru district (Western bank of Aswa River); Awere, Angagura, Kilak, Laguti, Acholibur, Pajule lapul, Puranga and Bolo in Pader district (Eastern bank of Aswa river); Palabek kal, Palabek Gem in Lamwo district (Eastern bank of Aswa River).

Nodding Syndrome clusters in Laguti and Atanga are along Ajan River which is a tributary of Aswa River; Okidi in Labongo-Amida; Pajimo and Tumangu –in Labongo-Layamo Sub Counties are drained by rivers such Lanyedyang and Awuc which are tributaries of Pager River [20].

Knox described a cluster as a series of cases that are delimited both temporarily and geographically; this may be applied to an illness that may appear in clustered form or that is of such size and concentration that is highly unlikely to be a product of chance [7]. Indeed the occurrence of NS in these specific locations and number of cases found is certainly not by chance.

Another researcher in occupational lung diseases stated that in a disease cluster, a case should be related through biological and/or social mechanisms or may have a relationship with a specific events or circumstances [8].

Figure 3: Map of Uganda showing NS clusters in relations to the river network in the Acholi sub region [20]

Nodding syndrome clusters along the major rivers in Northern Uganda

The findings observed among the probable cases of NS in the Acholi sub-region is that they occur among specific age groups (5-15 years) and in specific locations and mainly along the 2 major rivers (Pager and Aswa) (Maps in Figures 1, 2 & 3). Previous studies have indicated and confirmed that more cases were found in families where there was already a case of NS. This therefore perhaps represented the biological and social relationships of Nodding Syndrome in the region [6, 10,12].

Knox called this tendency towards grouping of many diseases in time and space, “clustering”. Thus clustering is the regular tendency of a single/ or many diseases to present themselves irregularly in time and space once the population density and chances are accounted for [7]. Nodding Syndrome pattern of distribution has regional trends because it occurs in relation to geographic coordinates (Maps in Figs 1, 2, 3). However, since most cases of NS lived in the IDP camps, there is perhaps an indication that there is a relationship between NS and time; particularly IDP camp exposures [1, 4, 6, 9, 10, 11, 12].

It is our view that because of the clustering of NS, the identification of the pattern of clustering can facilitate the establishment of the original aetiological hypotheses [7, 8].

The present epidemiological study relied heavily on statistics for establishing and quantifying the relationships between the locations and occurrence of NS, and for attempting to establish whether or not there was an excessive number of NS occurring in a specific geographic area [7, 8].

In clustered disease, both retrospective and prospective studies are useful in discovering links between environmental exposures and a particular disease [7, 8]. These epidemiological studies are especially significant when they uncover very high incidence of an unusual disease in a target population [7, 8].

The standard guidelines and protocol for epidemiological studies are well documented [7] and in addition, the epidemiological evidence can only show that a risk factor may be associated with higher incidence of the disease in the population exposed to that risk factor. Thus, the higher the correlation, the more certain the association between the risk factor and the disease [7, 8, 9]. Furthermore, the study should determine what behavioural, environmental and health factors being studied are the possible risk or protective factors [7, 8, 9, 10, 11].

In an event that an inappropriate risk factor is chosen for an epidemiological study, an association may be found between an inappropriate factor and the disease because this factor is associated with another factor which is actually related to the disease, but which was not studied. In such an instance, the inappropriate factor becomes a confounding variable, because it distorts the interpretation of the results of the study [7, 8]. The occurrence of the Onchocerciasis in the region among NS may perhaps be one of the confounders to the risk factors to NS. This is because, many regions in Africa and particularly Uganda have had very high prevalence of Onchocerciasis but there has not been such clinical presentation of NS [9, 10, 13]. More so, there has always been Onchocerciasis in the Acholi sub-region right from the colonial times (1900) and the community have a local name for

Onchocerciasis “two ajonga miya” [10, 12]. It is therefore more likely, that NS may have resulted from a new factor which has plunged the sub-region as a result of perhaps environmental activities that has not yet been identified. Reports from Mulago Hospital, the National Referral and Makerere University Teaching Hospital where 24 children with NS were transferred from Kitgum for specialized investigations and treatment showed that only 3 children had the antibodies for Ochocerca volvulus [14]. This finding would make Onchocerciasis a less likely cause/risk factor of NS. It is the researchers’ view that the association between Onchocerciasis and NS therefore, seems a non-causal, but related phenomenon in the development of NS.

It is probable that the open mining system alleged to be taking place in the Karamoja region which is the water shed for the rivers in the Acholi sub-region may perhaps be the source of contamination of waters and environments of the population downstream. These contaminations got exposed to the children who already had a deranged metabolic condition and were unable to neutralise the effects of the contaminants [10, 12, 15, 16]. A case control study conducted by researchers at Gulu University showed that Children with NS were in a state of metabolic acidosis compared to their matched controls [10]. Several studies have already shown that metabolic acidosis undermines the ability of the human body from binding heavy metals. Acidotic and probably malnourished individuals may therefore develop complications even with the slightest change in the heavy metal concentration in the body [10, 17].

There are several reports from Uganda geological departments showing that on the slopes of Mount Moroto in the remote north-eastern corner of Uganda where most rivers in the Acholi sub-region originate, members of the Karamojong tribe, including children, mine for gold, phosphate and uranium in the parched red earth [15, 16]. Some researchers have argued that NS was a result of contamination of the environment by heavy metal which became exposed to the young population in this region [11, 12, 15]. They argued that heavy metal toxicity could result in damaged or reduced mental and central nervous function, lowered energy levels and damage to vital organs [18]. Furthermore, they observed that long-term exposure to heavy metal could result in slowly progressive muscular and neurological degenerative processes similar to Alzheimer's disease, Parkinson's disease, Muscular Dystrophy and Multiple Sclerosis [18]. Organophosphate poisoning, which can occur from pesticide or chemical weapon exposures or from open mines, could similarly manifest into lethargy, coma and seizures [18]. Previous studies have shown that if the enzyme Acetyl-cholinesterase was suppressed in the nervous

system such as in organophosphate poisoning, it could cause illness in animals and humans [18]. These arguments were derived from some of the typical presentation (signs and symptoms) of Nodding Syndrome that was observed in children in this region.

We recognised the fact that this epidemiological study was cross sectional and therefore it has its own limitations. In spite of our several postulations, follow up studies are underway to extensively examine the environmental factors contribution to NS including tests for heavy metals in the water, silk, fish and tree root in these rivers.

CONCLUSION:

Nodding Syndrome in the Acholi sub-region presents in clusters involving certain specific geographic locations. These geographic locations are on either sides of Aswa and Pager Rivers which have their source of water in the Karamoja region where there are suspected open mines with several minerals including Gold and Uranium. It is recommended that detailed analysis of water, silk, fish, barks of trees, roots and soil samples in the clustered areas be conducted. Samples for analysis should be collected along these rivers from the source in Karamoja to Amuru.

Conflict of interest: Authors declare no conflict of interest

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