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Chapter Title	Towards a Spatial-Temporal Model of Prevalence of Nodding Syndrome and Epilepsy	
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Abstract

Nodding syndrome is an emerging disease which have unknown transmission patterns and no properly established mechanisms for diagnosis leading to numerous hypothetical postulations. It has affected thousands of children in Uganda with debilitating effect and serious economic consequences. Spatial-temporal analysis may provide a quick mechanism to establish comparative understanding of the various hypotheses ascribed to nodding syndrome and any other emerging diseases with similar clinical manifestation. There is considerable suspicion that “nodding syndrome is a form of epilepsy”, a hypothesis that has hardly been investigated in literature. The *aim* of the study described in this paper is to establish spatial-temporal relationships between ailments diagnosed as nodding syndrome and ailments diagnosed as epilepsy. An *exploratory cross section* survey in three districts of Northern Uganda was done. Spatial data of health centers were recorded and ArcGIS was used for display. The *findings* show significant spatial-temporal correlation of diagnosis reporting of nodding syndrome to epilepsy. The regression statistics overall, epilepsy significantly ($p < 0.05$) ex-plains about 58% of Nodding syndrome variability. The F-statistic shows a very highly significant value ($p = 8.20481E-13$; $p < 0.05$), meaning that the output of the regression is not by chance.

Keywords (separated by '-')

Nodding syndrome - Emerging diseases - Surveillance - Spatial-temporal - Geographic information system

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Towards a Spatial-Temporal Model of Prevalence of Nodding Syndrome and Epilepsy

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Abstract. Nodding syndrome is an emerging disease which have unknown transmission patterns and no properly established mechanisms for diagnosis leading to numerous hypothetical postulations. It has affected thousands of children in Uganda with debilitating effect and serious economic consequences. Spatial-temporal analysis may provide a quick mechanism to establish comparative understanding of the various hypotheses ascribed to nodding syndrome and any other emerging diseases with similar clinical manifestation. There is considerable suspicion that "nodding syndrome is a form of epilepsy", a hypothesis that has hardly been investigated in literature. The *aim* of the study described in this paper is to establish spatial-temporal relationships between ailments diagnosed as nodding syndrome and ailments diagnosed as epilepsy. An *exploratory cross section* survey in three districts of Northern Uganda was done. Spatial data of health centers were recorded and ArcGIS was used for display. The *findings* show significant spatial-temporal correlation of diagnosis reporting of nodding syndrome to epilepsy. The regression statistics overall, epilepsy significantly ($p < 0.05$) ex-plains about 58% of Nodding syndrome variability. The F-statistic shows a very highly significant value ($p = 8.20481E-13$; $p < 0.05$), meaning that the output of the regression is not by chance. AQ1 AQ2

Keywords: Nodding syndrome · Emerging diseases · Surveillance · Spatial-temporal · Geographic information system

1 Introduction

Space-time mapping and analysis of disease data has historically involved the search for patterns in aggregated data to identify how regions of high and low risk change through time [16]. Mapping of space and time analysis of aggregated data has great value, but represents only a subset of space time epidemiologic applications. Technological advances for tracking and mapping individuals (e.g., global positioning systems) have introduced mobile populations as an important element in space time

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G. Mendy et al. (Eds.): AFRICOMM 2018, LNICST 275, pp. 1–11, 2019.
https://doi.org/10.1007/978-3-030-16042-5_7

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epidemiological modelling [19]. The importance mapping, place, and time came in light more than 200-years ago when Dr. John Snow modelled a map of cholera deaths in relation to London's water pumps. This was one of the first, and perhaps the most celebrated, disease maps model. His history of disease mapping is filled with examples of maps that helped provide etiological clues to diseases from cholera to lung cancer. With the help of his famous map model, Snow was not only able to track the source of what he called "the most terrible outbreak of cholera which ever occurred in this kingdom," but he was able to convince authorities to act against the disease (Snow 1855). Analyzing and mapping spatial and temporal dynamics of infectious diseases features mathematical and spatial modeling approaches that integrate applications from various fields such as geo-computation and simulation, spatial analytics, mathematics, statistics, epidemiology, and health policy [5] provides great insights to understanding disease outbreaks.

In recent years, transmission of diseases has exhibited new spatial and temporal patterns [20]. Emerging diseases like nodding syndrome with unknown transmission patterns and mechanisms for diagnosis are being discovered more often. There is therefore need to harness geographical information system (GIS) capabilities to establish insights into patterns of spatial transmission.

Nodding Syndrome is a childhood neurological disorder which affects communities in Northern Uganda [13]. It is a poorly understood neurologic disorder of unknown aetiology that affects children and adolescents in Africa [21]. It is an emerging illness that has eluded surveillance models in Africa for over six decades since its discovery in the 1960's [7, 14]. There is hardly any surveillance model for investigating spatial diffusion and supporting geographical knowledge on how to intervene on the outbreak of nodding syndrome. Many authors agree that its spatial diffusion patterns, and transmission models are not properly understood [18], the characteristics, risk factors as well as aetiological factors are also not well established [4, 15, 18] complicating surveillance efforts. Up to the year 2012, when the Ministry of Health Uganda recognized the ailment as a public health concern, it had affected estimated thousands of children in Northern Uganda [4, 10]. The surveillance form used in health centers and hospitals for Integrated Disease Surveillance and Response lacked provision for nodding syndrome for all the years before 2012. The ailment became endemic in the population and the disease reached a threshold after over a decade to warrant public health concern.

There is considerable suspicion that nodding syndrome is a form of epilepsy [6, 11, 18]. Much as these findings are of biological significance, there is limited literature on spatial models comparing spatial prevalence of nodding syndrome and associated epilepsy. The Ministry of Health of Uganda and partner organizations identified the gaps in knowledge of nodding syndrome that "the actual geographic coverage and distribution is not known, and that there is need for surveillance in other areas outside the current foci and the overlap of areas of distribution of nodding syndrome, etiological, potential risk factors and other information of interest [15]. Also, the burden of nodding syndrome in the currently reported three foci and surrounding areas are also not known. The increasing prevalence of nodding syndrome in northern Uganda has generated a wide range of speculations with respect to aetiology and natural history and best possible medical treatment for this mysterious seizure disorder. Despite in-depth

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investigations by the United States Centers for Disease Control and Prevention and the Ministry of Health in Uganda, agree that no clear causal factors have emerged [15].

The spatial epidemiological prevalence of nodding syndrome particularly in Northern Uganda is inaccurately presented by different organizations [1]. For instance, the independent charity organization; Kitgum District NGO Forum, which first announced the outbreak of nodding syndrome, estimates that as many as 5,000 children are infected by the disease in Kitgum district alone, while government officials report; there are only 3,200 infected children, Other scholars put the total number of cases of nodding syndrome in the 3 districts of study at 1,876 [9]. These news reports and some clinical scholarly research examined above, clearly lack systematic spatial and temporal analysis of nodding syndrome. Furthermore, many scholars believe that "nodding syndrome is a form of epilepsy" [8, 11, 14], and [12]. However, these reports and researches hardly critically examined the distribution of the two diseases over time in-order to contrast them and make spatial correlation to deduce conclusion and intervention plans.

The compelling issues of this paper therefore are: (i) The need to determine whether nodding syndrome is being reported by the different health facilities in Northern Uganda, (ii) The need to establish spatial prevalence of nodding syndrome reporting and spatial and model the overlapping (scaffolding) relationship between nodding syndrome and epilepsy; and (iii) Propose a method for surveillance mechanism for nodding syndrome. AQ3

2 Methodology

This paper is a cross section studies comparing spatial-temporal diagnoses of diseases identified as nodding syndrome and those that have been identified as epilepsy in three districts of Gulu, Omoro, and Kitgum in Northern Uganda. Purposive sampling of health centers was used to identify facilities that are relevant for the study. Twelve (12) health centers were identified for the study based on Ministry of Health IDSR (Integrated Disease Surveillance and Reporting tool). Two questionnaires were used for data collection with the first one designed for health workers interfacing with nodding syndrome patients. It was to elicit basic information on the gravity of nodding syndrome in the communities and also provide some statistical overview of patients attended to from a particular health center. The second was designed for health centers and hospitals data managers. It was particularly tailored to examine the depth of information available from a particular health center identified as receiving nodding syndrome victims. Environmental System Research Institute (ESRI) ArcView Software was used for analysis and display of the data on a map. ANOVA and Spreadsheet were used for trend and regression analysis. Analysis was done consecutively for five years to establish the spatio-temporal aspects.

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3 The Study Findings

We can observe that health centers, began reporting on nodding syndrome incidences especially in West of Aswa river basin in 2012. In Kitgum, Pajimo and Tumangu also began reporting around the same period. The Local NGO Hope for Humans was established in Odek because the cases were very many in the area and spear headed advocacy program about the outbreaks and scientific research.

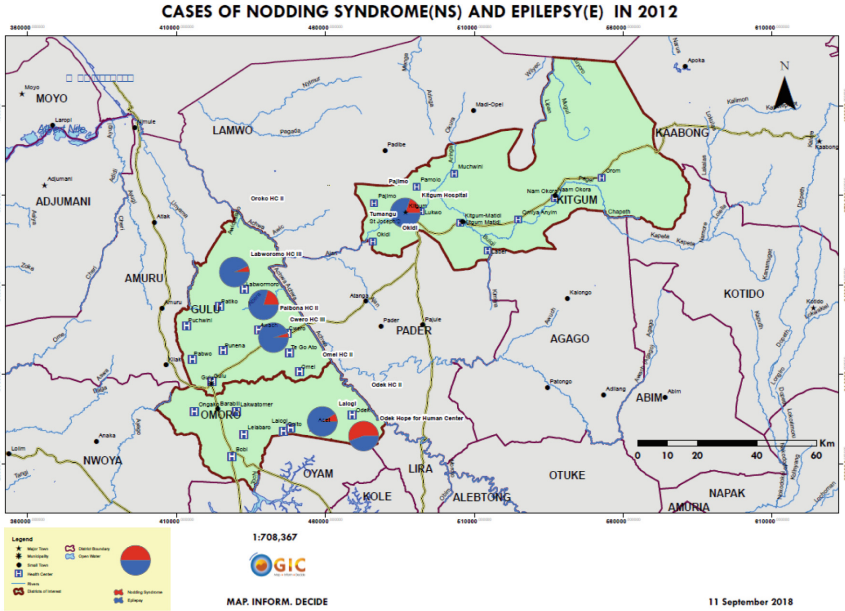

Fig. 1. A map of health centers reporting nodding syndrome and epilepsy in 2012

The number of health centers reporting the ailments increased in the following years mostly along the span of Aswa River. The patients that were in Omoro were referred to Hope for Human Centre which was thought to have better facilities and specialized in treatment of nodding syndrome patients. While others that were in Kitgum district were referred to Kitgum Hospital. Most health facilities however, continued recording epileptic also patients across the region. By the year 2016 (Fig. 2), the spatial-temporal reporting was widely spread across the three districts.

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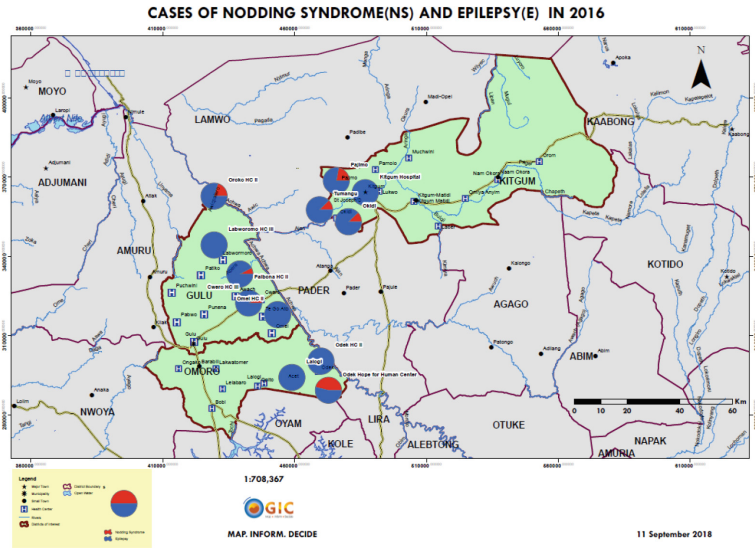

Fig. 2. A Map of health centres reporting nodding syndrome and epilepsy in 2016.

In 2017 (Fig. 3), it appears that diagnosis of nodding syndrome was very low across the region, however, the associated epilepsy were distributed across. On the other hand, the Referral Hospital in Kitgum and Hope for Human Centre had high number of diagnosis of epilepsy.

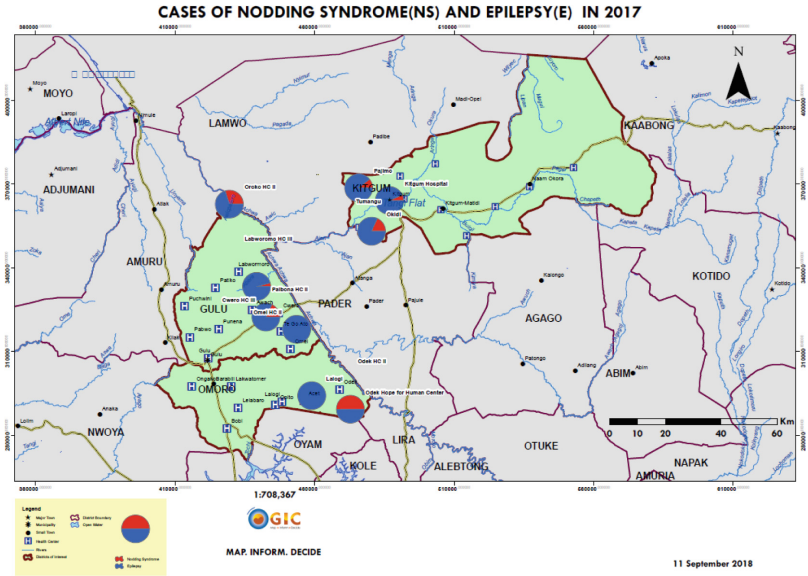

Fig. 3. A map of health centres reporting nodding syndrome and epilepsy in 2017

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4 Analysis and Discussions

A shown from Figs. 1, 2 and 3 the number of health centers reporting of nodding syndrome were rising. We can observe that the spatial-temporal prevalence of nodding syndrome and associated epilepsy were mimicking one another. The period between 2015 and 2017 is special in that there was massive Campaign for support to nodding syndrome victims. Since nodding syndrome manifests with epilepsy, the turn up of patients diagnosed as epilepsy other than nodding syndrome were exceedingly high with the peak of 7,725 patients. This also explains the anomaly in the reporting figures for nodding syndrome by the different organization partnering to provide health services in Northern Uganda (Fig. 4). AQ4

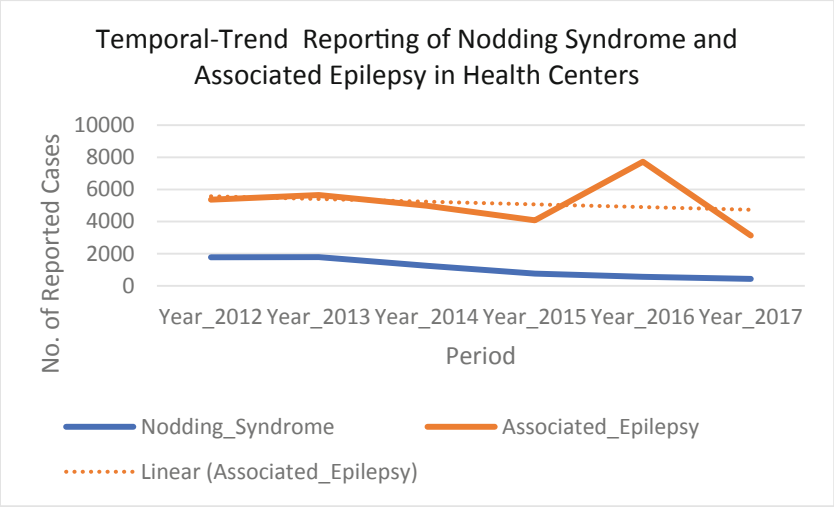

Fig. 4. Temporal Graph with line of best-fit showing Nodding syndrome & associated epilepsy reporting.

4.1 Data from Hope for Human Center (Odek)

Diagnoses data collected from Hope for Human (Fig. 5) Center provides a classical comparison of the two ailments. In September 2013 saw the diagnosis overlap one another (scaffold). Nodding syndrome dropped down epilepsy as the patients continue receiving treatment at Hope for Human Center. The patients that were originally diagnosed as having both nodding plus epilepsy improved and nod no more. Some recovered and left the treatment Center, however, some have remained epileptic.

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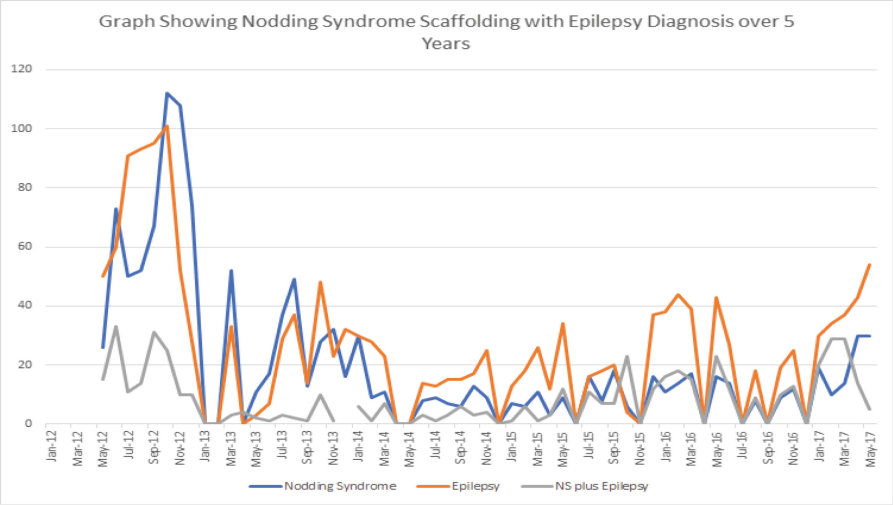

Fig. 5. Temporal scaffolding pattern of nodding syndrome and epilepsy

4.2 Scaffolding Model of Nodding Syndrome and Associated Epilepsy

Distinguishing nodding syndrome and epilepsy reporting shows some succinct details in that, there is scaffolding/ overlap between the two ailments. Much as epileptic conditions are clear, nodding is equally clear and it seems they influence each other. Figure 6 is an attempt to show distinctions and relationships between the two conditions. AQ5

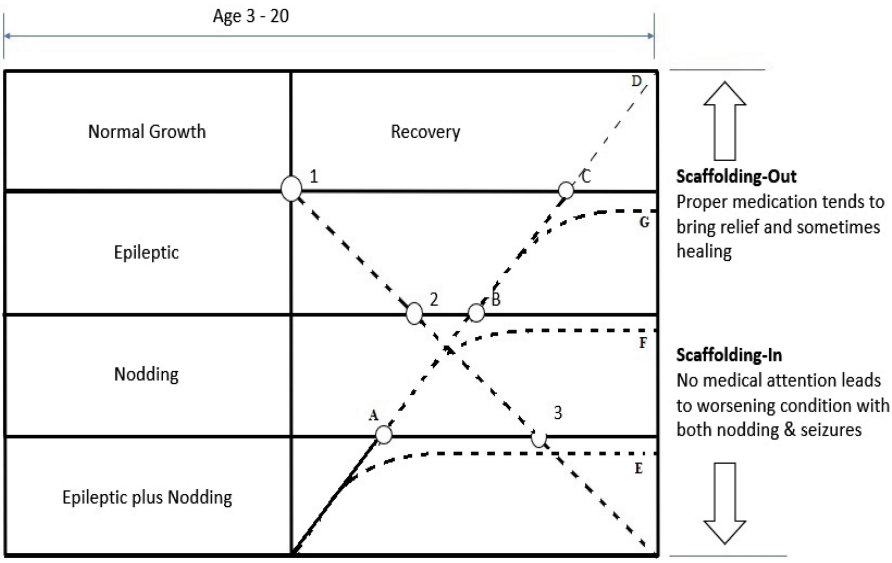

Fig. 6. Scaffolding model of nodding syndrome and epilepsy

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Scaffolding model postulates that a form of brain injury/infection manifesting with epileptic condition when left without proper medication progresses to nodding syndrome and can worsen to have both nodding plus epileptic seizures. However, when managed, the nodding process ceases followed by reduction in epileptic seizure and may recover to normality.

4.3 Scaffolding-In (Worsening Condition)

This consists of nodes (1, 2 &3) as condition worsens. A normally growing child comes in contact with nodding syndrome etiological agent (not yet identified), becomes epileptic. The epileptic condition overlaps to nodding (node 1) and when left unattended to overlaps to nodding plus seizures (node 3).

4.4 Scaffolding-Out (Recovery)

In the event that proper medical care is provided, seizures can be removed or reduced (node A). With continued medication, nodding also ceases (node B) and all epileptic conditions may be reduced (node C), and at times full recovery may result (node D). Some patients have only reduced nodding and epileptic conditions (node E) while others recover from nodding conditions (node G), but epileptic conditions remains unsolved problem (node G). Majority of the patients from Hope for Humans Center have fully recovered and have either returned home and were able to go back to school.

4.5 Regression Analysis

To evaluate the strength and nature of the association between epilepsy and Nodding Syndrome, Ordinary Least Squares regression was done with Nodding Syndrome being the dependent variable, and epilepsy the independent variable. The results of the regression are given in the Tables 1, 2 and 3.

Table 1. Regression statistics summary

Regression statistics	
Multiple R	0.763688212
R Square	0.583219685
Adjusted R Square	0.576155612
Standard error	16.07864554
Observations	61

From the regression statistics in Table 1, overall, epilepsy significantly ($p < 0.05$) explains about 58% of Nodding syndrome variability. This is given by the R^2 value (0.58).

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Table 2. Analysis of variance

	df	SS	MS	F	Significance F
Regression	1	21344.00476	21344.00476	82.56138826	8.20481E-13
Residual	59	15252.8477	258.5228424		
Total	60	36596.85246			

From the ANOVA results in Table 2, the F-statistic shows a very highly significant value ($p = 8.20481E-13$; $p < 0.05$), meaning that the output of the regression is not by chance. This means that epilepsy significantly influences the distribution of Nodding Syndrome, and this influence is not by chance.

Table 3 .

	Coefficients	Standard error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	−0.5720	3.0641	−0.1867	0.8525	−6.7032	5.5592	−6.7032	5.5592
Epilepsy (x)	0.7741	0.0852	9.0863	8.20481E-13	0.6036	0.9446	0.6036	0.9446

Results from Table 3 show that the contribution of epilepsy to Nodding Syndrome is highly significant ($p < 0.05$). The overall equation for this Epilepsy-NS association is given by Eq. (1). However, the intercept obtained is not reliable as it is statistically insignificant ($p = 0.8525 > 0.05$). From Eq. (1), it can be observed that overall, for every one unit increase in epilepsy, there is a 77% increase in Nodding Syndrome. This seemingly explains the relationship observed in (Fig. 6) where an increase in one disease resulted in an increase in the other. AQ6

$$y = -0.572 + 0.7741(x) \tag{1}$$

5 Conclusion

From this preliminary investigation, we have established that reporting on nodding syndrome by the different health facilities started in the year 2012 following recognition as a public health threat. Beyond 2012, no record exists in the reporting tools provided by Ministry of Health Uganda especially in the Integrated Disease Surveillance and Response (IDSR) form. In fact, there was no provision in the IDSR form beyond 2012.

As we can observe, the trend of prevalence of nodding syndrome and epilepsy over the period of four years were very much the similar. However, there was exceptional peak trend in associated epilepsy between 2015–2016 due to mass political assertion to intervene on the outbreak. Also, because nodding syndrome usually first manifests as

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epileptic conditions, the diagnosis and reporting in health facilities were not upright nodding syndrome, but rather epilepsy in the reporting tools provided by the Ministry of Health Uganda.

The study shows that there is scaffolding relationship in prevalence diagnosis of nodding syndrome and epilepsy especially with critical evaluation of data from Hope for Human Nodding Syndrome Center. The spatial-temporal analysis of diagnosis and reporting by the different health facilities, the study confirms that spatial-temporal distribution nodding syndrome is associated with spatial-temporal distribution of epileptic condition. This is also in line with other scientific establishment such as [6, 11, 18] and [8] through clinical studies which established that nodding syndrome is a form of epilepsy.

Therefore, we can affirm that due to relationships that exist as seen in scaffolding pattern, surveillance of nodding syndrome must go hand in hand with surveillance of epilepsy. The existing Integrated Disease Surveillance mechanisms can be improved to consider nodding syndrome, epilepsy as well as conditions that manifest both. And when there appears to be an outbreak of epilepsy, it may be a sign that infection that may result to nodding syndrome is in a community.

At the same time, we can also affirm that in the event of occurrence of emerging disease, when there is no established clinical diagnosis, geographical information systems (GIS) approaches can be effective alternative investigation mechanisms to establish relationships between hypothetically similar outbreaks.

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