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Exploring the Nutrition status of Children affected by Nodding Syndrome (NS) in Western Equatoria State of South Sudan

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2004

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Abstract

Exploring the Nutrition status of Children affected by Nodding Syndrome (NS) in Western Equatoria State of South Sudan

By Godwin Mindra

Nodding Syndrome (NS) is a novel form of epilepsy seen predominantly among children aged 5-18 years and characterized by head nodding, cognitive impairment, mental retardation and physical growth deterioration. To date the cause of nodding syndrome remains unknown. Apart from South Sudan, nodding syndrome has been reported in northern Uganda, bordering South Sudan to the South and southern Tanzania. The condition's characteristic head nodding is usually stimulated by either food and/or cold weather. The age at onset of nodding syndrome is commonly reported in children between 3 and 5 years but observed current age of cases range up to 23 years in Mundri and Maridi counties of Western Equatoria State.

The purpose of this study was to investigate the nutrition status of children affected by nodding syndrome exploring acute and chronic (stunting) nutrition patterns. Case-control technique was used to investigate the growth pattern of children affected by nodding syndrome. Anthropometric measurements were used to assess nutritional status in cases and controls. Twenty-three percent (23.7%) of all nodding syndrome cases were severely stunted (HFA z-score <-3) while the rate of wasting in nodding syndrome cases and their controls was not different (p=0.06). Nodding syndrome cases enrolled in the study showed strong correlation (r=0.41) between duration of the condition and stunting level.

Chronic malnutrition (stunting) is found to be frequent in children affected by nodding syndrome enrolled in the study. Critical to the management of children with nodding syndrome is targeted feeding program, education to parents on appropriate feeding of children, improve hygiene and sanitation, control of seizures and provide psychosocial support to children and parents.

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I would like to thank my mentor Dr Carlos Navarro-Colorado and the entire team at the International Emergency and Refugee Health Branch of the Centers for Disease Control and Prevention (CDC) whose work and support demonstrated to me that the plight of children affected by nodding syndrome transcends academia and provides a quest of our time.

The children and parents in Mundri and Maridi counties of South Sudan couldn't have gone unnoticed by their kindness in participating in the nodding syndrome investigation conducted in Western Equatoria State in May/June 2011 – thank you all.

Last but not the least I would like to thank my wife Florence and children Adrian, Archie, Ruth and Ariel for their love and patience while I was away from my paternal responsibilities. God couldn't have been more kind to me!

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ABBREVIATIONS

CES	Central Equatoria State
CDC	Centers for Disease Control and Prevention
CPA	Comprehensive Peace Agreement
DRC	Democratic Republic of Congo
GoSS	Government of Southern Sudan
HD	Head Nodding
IDP	Internally Displaced People
IERHB	International Emergency and Refugee Health branch
IRB	Institutional Review Board
LRA	Lord's Resistance Army
MoH	Ministry of Health
MUAC	Mid-Upper Arm Circumference
NCHS	National Center for Health Statistics
ND	Nodding Disease
NS	Nodding Syndrome
RSS	Republic of South Sudan
SS	South Sudan
SSHHS	South Sudan Household Health Survey
UNICEF	United Nations Children's Fund
US	United States
WES	Western Equatoria state
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1. BACKGROUND

Nodding Syndrome (NS) is described as an epileptic seizure disorder in various geographic areas of sub-Saharan Africa. In 1962 the first description of several children with attacks of 'head nodding' in Mahenge, a village of southern Tanzania, was made *(1)*. Winkler et al. in Tanzania provided a clinical classification of seizures, semiology and socio-cultural aspects and suggested it was a syndrome (referred to as "head-nodding syndrome") and a form of epilepsy *(2)*. In 2009 the media reports described a rare and unexplained brain disease affecting hundreds of children in Northern Uganda characterized by head nodding and seizures and victims become physically and mentally stunted while others die *(3)*. Kaiser et al, in 2009, referred to the phenomenon of head nodding as possibly constituting a feature of an epileptic syndrome caused by O. *volvulus (4)*.

A missionary doctor working for The Samaritans' Purse (a faith-based medical relief organization) in Southern Sudan in the mid 1990s, notably when the civil war was at its peak in the Country, described several children with nodding syndrome in Lui and Amadi villages of Mundri East county of Western Equatoria State. In 2003 reports to the World Health Organization (WHO) estimated 300 children affected by nodding syndrome in Western Equatoria State *(5)*.

Head nodding is often described as triggered by the presence of food or exposure to cold *(6,7)*. The nodding is typically characterized by repetitive bobbing or

nodding of the head, sometimes associated with drooling of saliva, loss of muscle tone in the trunk and upper extremities with or without loss of consciousness during the nodding episodes *(8)*. The syndrome has been described to be progressive, with gradual neurological deterioration and development of additional seizure types, developmental regression, cognitive decline, mental retardation and finally death either due to progressive deterioration and/or trauma due to seizures.

The Republic of South Sudan (RSS) was established on the 9th of July 2011 based on people's majority vote that brought to an end over five decades of hostilities between North and South Sudan. The civil war characterised by the use of light and heavy weaponries, indiscriminate aerial bombardment and landmine plantations. The war displaced over 4 million of the Country's current estimated 10 million people (2008 census), disrupted socio-economic services and systems, and extracted a heavy toll on the survival and well-being of South Sudanese, especially children. The 2005 Comprehensive Peace Agreement (CPA) provided a period of relative stability with thousands of displaced person returning to their homes while cross border activities with neighbouring countries like Uganda and Kenya (South), Ethiopia (East), Sudan (North), Central African Republic and Democratic Republic of Congo (West) heightened. The 2010 South Sudan Household Health Survey (SSHHS) showed improvements in the situation of children during the period 2006-2010. Infant and under-five mortality rates decreased from 102 to 84 and 135 to 106 per 1,000 live births respectively. Recorded measles cases decreased from nearly 2,000 to below 100 per annum, and the Country has been polio free since 2009. The prevalence of underweight

dropped from 32.8% to 28%, and stunting reduced from 33.4% to 25.0%. Access to improved sources of drinking water increased from 48.3% to 68.7 % and improved sanitation facilities from 6.4% to 12.7%.

The cause of nodding syndrome remains largely unknown nonetheless several factors including exposure to munitions, prior history of measles infection, consumption of baboon meat and sorghum, genetic predisposition and micronutrient deficiencies are being investigated for association. A significant association of nodding syndrome with detection of O. volvulus microfilariae in skin snips was observed in a case-control study in Sudan in 2001 – 2002, and in an assessment in Tanzania (84% of 62 children with NS had microfilariae or O. volvulus nucleic acid in skin snips) which is in common with studies that have identified association between Onchocerciasis and epilepsy in general *(9)*. A study conducted in parts of Southern Sudan estimated prevalence of Onchocerciasis volvulus in general population to be 25% while in children is estimated at 10.8% *(10)*. In southern Tanzania where cases of nodding syndrome have been reported the prevalence of Onchocerciasis volvulus is estimated in the general population at 58.1%, no age-specific prevalence estimation for children was provided *(11)*.

1.2. PROBLEM STATEMENT

Nodding syndrome is a new disease with unknown etiology, prevention and treatment but affects a large number of children. However the description of an association with malnutrition and knowledge of the mechanisms that lead to

malnutrition could facilitate care, prevention and treatment of those affected with nodding syndrome.

1.3. PURPOSE OF THE STUDY

The purpose of this study is to investigate the nutrition status in children affected of nodding syndrome exploring, acute and chronic (growth) nutrition patterns. This study will aim at exploring what associations exist between the nutrition status of children affected by nodding syndrome and nodding syndrome.

1.4 SPECIFIC STUDY OBJECTIVES

This study will seek to:

a) Understand the relation between nutrition status and nodding syndrome in children affected.
b) Provide recommendations on appropriate feeding and care practices for the children affected at family, community and institutional levels, if nodding syndrome is found to affect their nutritional status.

1.5. SIGNIFICANCE OF THE STUDY

This study is expected to contribute to the existing knowledge base on nodding syndrome especially on the nutrition status of children affected and generate recommendations expected to be helpful in the care of children affected at family, community and institutional level. This thesis is also expected to provide information for further research on nodding disease.

CHAPTER 2

COMPREHENSIVE LITERATURE REVIEW

2.1 RATIONAL AND CONCEPT

This literature review looked at the relationship between chronic malnutrition defined as failure to attain expected height for age measured in terms of height for age and nodding syndrome; it will also explore linkages between acute malnutrition defined as a weight-for-height of two standard deviations below reference points in the current revision of WHO growth standards *(12)*. In children, the presence or absence of acute malnutrition is measured by taking body parameters which includes the mid-upper arm circumference (MUAC), weight for expected height and age of the child. For this review and study height and weight will be the parameters used to establish acute and chronic malnutrition. At the individual level, physical status reflects functional aspects of development and performance and is a good proxy for overall well-being. At the population level, socio-economists have suggested that stature is an excellent indicator of the standard of living and wellbeing *(13)*.

2.2 UNDERSTANDING THE CHARACTERISTICS OF NODDING SYNDROME

It is unclear if nodding syndrome represents a form of Epilepsy. Globally epilepsy is a major health and mental health disorder leading to significant deleterious personal, familial and social consequences. Various population-based studies in western countries have focused on the prevalence and epidemiology of epilepsy,

thus, enhancing the body of knowledge on epilepsy occurrence in developed countries compared to studies conducted in developing countries, specifically in sub-Saharan Africa (*14*, *15*, *16*, *17*). Epilepsy and seizure-like conditions undoubtedly constitute a major problem in developing countries (for example Nigeria, Liberia, Tanzania and Uganda) with the prevalence of these conditions shown to be much higher than in industrialized countries (*18*). Even when epilepsy is reported to have been around for a long time, little is known about its current prevalence and distribution in rural areas on the African continent (*19*).

Seizures of different types affect over 20 million children worldwide most times described as heterogeneous collection of syndromes invariably characterized by additional conditions that coexist with seizures *(20)*. Seizures in both children and adults are associated with cognitive, emotional and behavioral co-morbidities. Para et al. 2001 *(21)* classify seizures generally as partial or focal and generalized and continue to indicate that involvement of both cerebral hemispheres describes the nature of generalized seizures while focal seizures only involve part of the brain and its manifestation is noted in corresponding body part(s) controlled by that portion of the brain. Seizures may or not produce loss of consciousness which may last for varied lengths of time either for long periods of time or temporarily, and are sub-categorized into generalized tonic-clonic, myoclonic, absence, or atonic subtypes *(22)*.

Investigations conducted in South Sudan and Tanzania have invariably described Nodding syndrome as a neurological condition that is associated with seizures and cognitive retardation *(23,24)*. Head nodding (HN) or bobbing is defined as a repetitive short loss of neck muscle tone resulting in head nodding, may or may

not be associated with a short loss of muscle tone of the upper extremities and impairment of consciousness. Nyungura et al. *(25)* acknowledged that nodding syndrome is a progressive mentally debilitating condition that commonly affects children in South Sudan, Uganda and Northern Tanzania. Frequently nodding syndrome is defined as a condition associated with mental retardation or stunted growth more or less describing the progressive nature of the condition *(26)*.

In some areas of Uganda an entity termed the 'Nakalanga syndrome' consisting of epilepsy, stunted growth and mental retardation, reminiscent of the "nodding disease" in South Sudan has been described *(27)*. Nakalanga Syndrome was first noticed in the 1950s as a condition that affected teenagers at an average age of 15 years and was invariably common in areas with high prevalence of Onchocerciasis Volvulus along the River Nile. When Onchocerciasis was effectively controlled in these areas through larviciding no new cases of Nakalanga Syndrome were noted. The association between Nakalanga Syndrome and Onchocerciasis is largely a postulation since no temporal association has been shown.

A poorly understood head-shaking condition has been described in horses as largely a natural behavioral pattern with unknown etiology *(28)*. This condition is exacerbated by warm and sunny weather condition including riding the horse under trees. Both medical (for allergic rhinitis) and surgical (trigeminal nerve block) treatment protocols have been deployed in an attempt to alleviate the condition but with little success.

There is a grey-zone in the description and distinction between epilepsy and the Nodding Syndrome much as several investigations, literature reviews and studies

have been conducted; this may be in part because studies have not been efficient enough to address and disaggregate diseases confused with nodding syndrome. Most studies conducted have not directly observed children with head nodding but rather relied on description of the condition from parents and caretakers, and children with nodding syndrome tend to present with epilepsy-like features which has led to unclear definition of nodding syndrome.

2.3 ETIOLOGY OF NODDING SYNDROME

The cause of nodding syndrome remains hitherto unknown although the condition is increasingly being associated with high prevalence of Onchocerciasis volvulus *(29)*. The association between nodding syndrome and Onchocerciasis volvulus is a causal hypothesis that would require isolation of filarial worms or its products from the brains of children. Studies, as conducted by Winkle et al. *(24)*, aimed at isolating the parasite in the central nervous system will be helpful in the identification of the cause and improve the outcome of the disease management.

Other etiological factors being investigated include exposure to heavy metals like mercury and lead, deficiency of vitamin B6, genetically related causes and nodding syndrome being a sequel of infectious diseases like measles and malaria.

2.4 NODDING SYNDROME IN WESTERN EQUATORIA STATE OF SOUTH SUDAN

Western Equatoria State (WES) is one of the 10 States of South Sudan that shares borders with the Democratic Republic of Congo (DRC) to the South, the Republic of Central Africa to West, Lakes State to the North and internally Central Equatoria State to the East. Western Equatoria State has an estimated population

of 700,000 people (census 2008) spread out in the 10 counties of the State covering an estimated area of 79,319 Sq km *(30)*. Following the signing of the Comprehensive Peace Agreement (CPA) in 2005 the State registered massive influx of returnees and Internally Displaced Persons (IDPs) as a result of incursions on the civilians by the Lord's Resistance Army (LRA), a self styled rebel group. Besides the post-peace agreement displacements, during the 2 decades of civil war over 80% of the indigenous population of the State was displaced into neighboring States (CES, Lakes) and countries (Uganda, DR Congo and Central African Republic).

Much as the State Ministry of Health is rebuilding the health information system, anecdotal surveillance reports have indicated that most of the cases of nodding syndrome in WES have been reported from the Eastern counties of the State. The map in **appendix C** shows that the State's watershed (rivers and water bodies) is largely found in its eastern region.

The World Health Organization (WHO) conducted a detailed nodding syndrome investigation in Southern Sudan in 2001 the result of which hypothesized that nodding syndrome was not due to infection with *T. brucei gambiense*, *W. bancrofti* or *L. loa*. This conclusion is contrary to the observations of a study conducted in South Sudan which noted positive skin snips and higher microfilaria loads of *O. volvulus* in children with nodding syndrome compared to children without the condition. Subsequent observational investigations (case control and cross-sectional studies) conducted in 2002 by WHO did not find environmental pollutants, chemical agents or food toxins as possible causes for

the seizures while EEG of 31 children studied showed progressive epileptic encephalopathy in victims of nodding syndrome *(31)*.

2.5 INTERACTION BETWEEN NUTRITION, PHYSICAL AND COGNITIVE DEVELOPMENT

There is evidence which supports that undernutrition in early childhood is associated with delayed growth, mental and cognitive milestone attainment in children *(32)*. Malnutrition is endemic to Western Equatoria and South Sudan given over two decades of civil unrest with massive population displacements and uncontained food insecurity which increases the vulnerability of children to cognitive impairment *(33)*. Children who are undernourished have higher chances of diminished functionality at adulthood because of the damage caused during infancy this includes poor performance at school and low ability to socialize *(34)*.

Studies have indicated that malnutrition reduces seizure threshold therefore making the brain more susceptible to seizures *(35)*. These findings underscore the need for a better understanding of the underlying patho-physiology of seizures and its relation to malnutrition.

Several authors, Reilly et al. 1996 *(36),* Stally et al. 1993 *(37)* and Thommessan et al. 1991 *(38)* have indicated the presence of feeding challenges and undernutrition in mentally and physically challenged children. This in part is due to intake being reduced because of anorexia, chewing, vomiting and swallowing difficulties. Since children with epilepsy gradually become mentally and physically challenged if seizures are not adequately controlled; it is possible that

this state is linked to malnutrition associated with feeding challenges, inappropriate choices of foods and unbalanced effects of energy needs due to physical inactivity and drugs. It is expected that this insufficient nutritional status would then worsen the children's health, specifically their immune status *(39)*. Since nodding syndrome is frequently described as a seizure-like condition it is possible that malnutrition is a consequence of the condition due to feeding challenges.

Commonly used neurological medicines including anticonvulsants have an effect on the nutritional status of the recipients as indicated by their effect on the appetite and control of energy balance with a resultant decrease (topiramate) or increase (Carbamazepine and Valproate) of body weight. Phenytoin, Phenobarbitone and Carbamazepine have been shown to interfere with vitamin D metabolism and increase the risk of osteopenia and osteoporosis *(40)*.

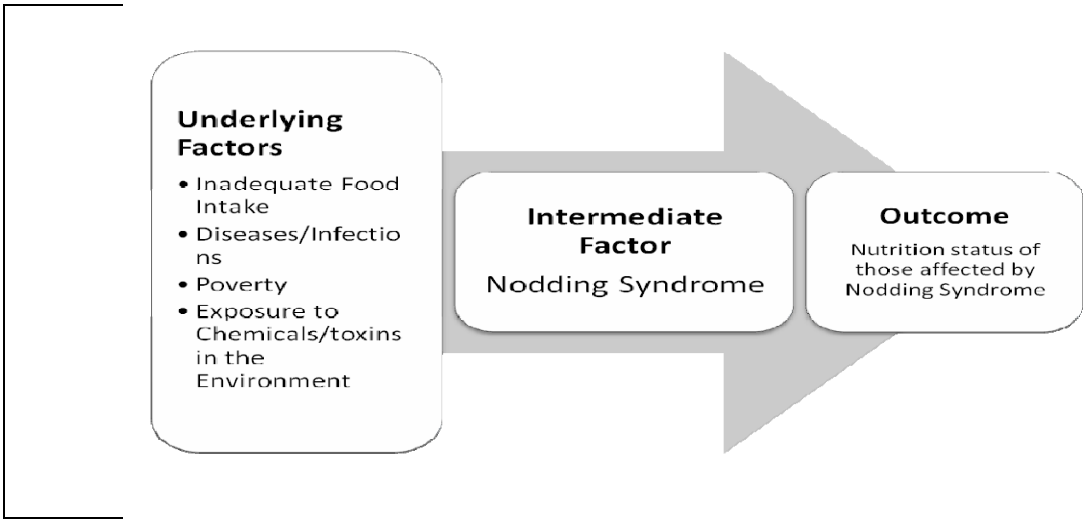
2.6 EMERGING AND UNMET NEEDS OF NODDING SYNDROME

Several investigations and reports have not been able to categorically define the cause of nodding syndrome which has a bearing on the management of children affected. Hitherto, several studies have presented description of nodding diseases as stated in the following studies: Aall-Jilek, LM – Northern Tanzania *(1)*; Lacey, M. *(5);* Mickey et al –Southern Sudan *(31)* and Winkler et al – Southern Tanzania *(2)*. The authors of these studies acknowledged that nodding syndrome is a seizure-like condition whose etiology is not yet known and is a condition that poses physical, social and mental challenge to the victims. Despite this glaring

evidence, there has been no analysis exploring direct association between nodding syndrome and the nutrition status of those affected.

2.6.1 Study Conceptual Framework

This study seeks to explore the relationship between nodding syndrome and the nutritional status of children affected. The conceptual framework below postulates our understanding of the relationship between nodding syndrome and the nutritional status of those affected by the condition.



Analysis of Previous Studies:

Studies by various authors have in one way or the other linked nodding syndrome to malnutrition in those affected as indicated in the table below. The premise of this thesis is to establish whether nodding syndrome per se leads to malnutrition or malnutrition worsens the picture of nodding in those affected. While conducting this study we are aware of underlying factors which could act through nodding syndrome as an intermediately factor affecting the nutritional status of those affected

Summary of Past Nodding Disease Studies and their Relationship to the Nutrition Status of those affected

Year of Study	Country	Study Region	Description	Were there anthropometric measurements taken? (Yes/No)	If yes, what is/are the finding(s)	Any Nutrition Specific Recommendation(s)
1962, 1964 and 1965	Tanzania	Southern Region, Mahenge are of Ulanga District.	Described head nodding which typically comes before grand-mal seizures.	No	None	None
1983	Liberia	Among Bassa, Kpelle area	Provided a description similar to that of Nodding Syndrome.	No	None	None
1990	Sudan	Greater Mundri	Head nodding in children associated with presence of food or cold.	No	None	None
2000	Uganda	Western Uganda; Bundibugyo district	Occurrence of head nodding in an area which has a high prevalence of Onchocerciasis volvulus.	No	None	None

2001/ 2003	South Sudan	Lui and Amadi areas of Mundri	Provided a description of the characteristics of head nodding being associated with stunting, growth and mental retardation.	No	Described children affected by nodding syndrome as being below average height for age, but no measurements taken.	Provide nutrition support to children affected and where possible supplementar y feeding programs.
2008/ 2010	Tanzania	Southern Region, Mahenge are of Ulanga District.	Clinical description of nodding syndrome and social cultural factors.	None	None	Recommende d care and support for children and families affected including nutritional care.

Anecdotal reports have also indicated the isolation of children affected by nodding syndrome in homes and communities for fear of cross transmission. In general these reports (community and program reports) highlight the need for concerted effect not only to identify the causative factor(s) but institute effective community educational interventions to improve the current understanding of nodding syndrome and to diminish social discrimination and misconceptions against the condition and those affected.

Egdell & Stanfield *(41)* argues that disorders of the nervous system in children in the tropics have received very superficial and sporadic study despite the fact that children form a large proportion of the population of developing countries. In addition these children are exposed to more frequent environmental hazards, such as birth trauma, acquired infection, malnutrition, hyperthermia, and water and electrolyte disturbances. Late or ineffective treatment of these conditions adds to the toll of brain-damaged children among the survivors while the introduction of effective treatment of formerly debilitating conditions like epilepsy inevitably results in the rehabilitation of affected children or young adults. Much as strides have been made in the rehabilitation of children who are mentally and physically challenged gaps still exist in the social and health systems which are already over stretched. This situation coupled with existing priorities lead to inadequate attention being paid to emerging challenges like nodding syndrome whose etiology and treatment is not clearly understood.

In conclusion these findings provide the evidence that seizures and malnutrition affect the outcome of mental development and the prognosis of physical and

cognitive development of individuals especially children who are vulnerable. Studies have indicated that seizures in children reduce their ability to interact, feed and provide formidable immunity to common ailments hence increasing vulnerability to environmental changes, particularly when these changes occur during the period of early brain growth and infancy. In this review nodding syndrome has been described invariably to be associated with seizures but no literature has linked the nutrition status of children affected and nodding syndrome. The link between nutrition and seizures has only been elaborately defined in the likelihood of seizures, brain damage and mental disorders increasing the chances of malnutrition either through vulnerability to infections or by impairing the cognition of the victims hence inability to socialize and feed adequately. Nonetheless the association of both conditions, seizures and malnutrition, can be extremely important and relevant to public health, as the number of children affected by conditions such as fever, trauma, and infectious diseases, associated with malnutrition is very high.

This study provides opportunity for further work on the understanding of the link between nutrition status of children affected by nodding syndrome and nodding syndrome. It is possible that patients who have a greater number of seizures may have suffered from malnutrition or malnutrition could be a resultant effect of the seizures and their inability to socialize, feed and be supported in the community.

In addition to exploring the relationship between the nutrition status of children affected by nodding syndrome and nodding syndrome, further analysis of whether the malnutrition seen in these children is due to dietary deficits (lack of food), or to other causes like a developmental deficit linked to hormonal causes or metabolic syndromes secondary to nodding syndrome will be necessary.

Thus a better understanding of the relationship between seizures and nutrition status of the victims is required which will also provide the opportunity for improved care, treatment and prevention of malnutrition for millions of children with seizures who may have an increased risk of malnutrition and vulnerability to infections.

CHAPTER 3

PROJECT CONTENT

3.1 STUDY DESIGN

The premise of this study is an observational case control study conducted May/June of 2011 in the counties of Mundri and Maridi of South Sudan. The protocol for this study was developed and implemented jointly by experts from the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and United Nations Children Fund (UNICEF) on the request of Ministry Of Health/Government of South Sudan. A non random sampling method was used in the selection of clusters of cases of suspected nodding syndrome because of existing surveillance report which indicate aggregation of cases in particular Counties, available time to carry out the investigation and insecurity which did not allow for selection of the entire region affected. Participants were selected into matched case-control and case series study design.

The study used case control and series approaches during the investigation in South Sudan; qualitative techniques like focused group discussions, community member interviews and observations were also conducted to gather more information and enrich findings.

3.1.1 Case definition

Participants were chosen into the study depending on where they met the case definition or not as indicated below.

For the purpose of the investigation an operational definition was formulated which defines a clinical case as follows : Is a subject between 5 years and 18 years, who was previously developmentally normal, has observed head nodding, and at least one other neurological and/or cognitive deficit. Loss of impairment of consciousness may or may not be present. Additional partial or generalized non-Head nodding epileptic seizures may or may not be present.

3.1.2 Participants' description, source population and catchment area

Children between 5 and 18 years of age with clinically defined nodding syndrome from the counties of Maridi, Mundri East and West in Western Equatoria state, were screened and selected into the study. The subjects were identified from clinics as well as at the community level through community-based active case finding. Presently available and updated line listing obtained from surveillance reports was used as a guide to determine case loads and sample sizes in the Communities sampled.

3.2 PARTICIPANT INCLUSION CRITERIA

3.2.1 Definition of a case

All children identified at clinic level and/or community level in the region will be eligible to enter into the assessments if they met the following inclusion criteria:

a. Head nodding episodes and/or any type of seizure activity. All enrolled children should have demonstrated head nodding or other seizures as reported by parent(s) or adult caretaker who has lived with the child.

b. Are attended by a caregiver who is/are able to understand and give informed consent

c. Definitive neurological abnormalities include loss of developmental milestones, other witnessed seizures, objective neurological exam findings such as spasticity, ataxia, or other clear neurological signs.

d. Developmentally normal before the onset of Nodding Syndrome.

3.2.2 Definition of a control

Friend control was a child within 2 years of a matched case in a ratio of 1:1 (1 control for every case) selected based on the following criteria:

a. No evidence of head nodding, or seizure, or any other neurological abnormality.

b. Who lives in the same village as the case (friend control)

c. From a household with no cases of nodding syndrome.

3.3 SAMPLING, SAMPLE SIZE AND STATISTICAL POWER

Investigators proposed 35 cases and 35 controls with a total of 70 participants for the case control investigations. Every alternate case from among the 35 cases was included for the case series clinical and neurological examination making a sample of 18 for the descriptive series. This resulted into 18 additional nodding syndrome cases above 18 years of age constituting the case series group, selected using the same case definitions used in the selection of cases in the case-control arm of the study.

Sample size calculations were made using Epi-info 6. All sample size calculations were based on an alpha of 0.05 and 90% power.

3.3.1 Sampling aspects

Sampling universe	All children with Nodding Syndrome identified in the participating clinic or participating community
Sampling frame	List of all children drawn after active case finding at the community level and the clinic level
Sampling unit	Child between 5 and 18 years with Nodding Syndrome (and friend control)
Respondent	Care-giver of the participant (case or control)
Subject	Child 5 to 18 years old with Nodding Syndrome and a friend control
Unit of analyses	Child with Nodding Syndrome included and compared to a matched control.

3.3.2 Recruitment and Enrollment

All children identified at the clinics and/or communities in the region were eligible to enter into the interview if they met the inclusion criteria after completing the Screening form and addressing the exclusion criteria.

Cases enrolled were screened using the case definition tool and matched to a control friend within two years of age difference. Every eligible case was included for the

case control investigation and every other case in which consent was obtained was included in the case series assessment.

3.3.3 Variables

The following variables were included in the analysis of data obtained:

a) Descriptive variables for both cases and controls: Age, Sex, Residence, Family demographics, Socio-economic variables, date (month and year) of onset of the disease, past medical history and nutritional/feeding habits.

b) Anthropometric measurements: Height, weight, presence of edema

c) Comparison variables: all the above listed descriptive variables were compared among nodding syndrome cases and their controls.

3.3.4 Study Instrument(s)

During the study information was collected using questionnaires which were developed and tested in field with surveillances officers, community members and Ministry of health officials. The questionnaires were used as follows besides collecting data for the study.

a) Clinical case series description and

b) Case control investigation **(See appendix E)**

3.4 DATA HANDLING AND ANALYSIS

3.4.1 Qualitative Data Analysis

Data analysis is the systematic organization and synthesis of research data. Qualitative data on gender and history of going hungry were categorized and

analyzed using EpiInfo statistical software 3.5.3.

To ensure validity and reduce confounding during design of the study restriction by age and location was used in the selection of participants. In the data analysis stage statistical methods and stratification by sex were used so as to reduce bias and increase reliability of results.

3.4.2 Quantitative Data Analysis:

Numerical data collected during the study were analyzed quantitatively based on statistical data analysis approaches that included frequency distributions, measurement of central tendencies (graphs, tables, pie-charts and histograms).

EpiInfo version 3.5.3 was used for data entry and preliminary data analyses and additional data analyses was undertaken using SAS version 9.0. Resulting inferences might generate further hypotheses for later inquiry.

3.5 DESIGN VALIDITY

3.5.1 Internal validity

Burns and Groove, 2005 *(42)* point out that a research instrument is valid if it actually measures what it is supposed to measure and when the data collected through it accurately represents the respondents' opinion and not a result of extraneous factors. To ensure internal validity of the research instrument (questionnaire) used in this study, the content was discussed with technical team the ministry of health at both state and central level and WHO to ensure clarity, relevance and removal of ambiguity.

3.5.2 External validity

Fisher and Foriett, 2002 *(43)* define external validity as the extent to which the information gathered from the selected sample is representative of an external population of the area under study. Investigators used existing guidelines to determine the sample size. However for this study samples would not be representative because selection was not random and hence findings may not be generalized. Findings from this study will only be applicable to the study population from which samples have been drawn.

3.5.3 Reliability

According to Polit and Beck, 2004 *(44)* reliability is the dependability or trustworthiness of research results or the degree to which a measuring instrument consistently measures what it is supposed to measure and is consistently associated with the methods used to measure research variables. To this effect, in this study, reliability of the data collected will be tested using Cronbach's alpha ($\alpha = 0.05$) method as provided by SAS and EPI-Info version 3.5.3 to determine how well all items in the test relate to all other items and to the total test. Reliability is compromised in cross-sectional studies like this one when respondents experience recall bias, do not understand questions and/or do not feel motivated by the question because it benefits him/her less. In this study matched cases to controls, structured interview questionnaire and face-face interviews were used to increase reliability.

3.6 ETHICAL CONSIDERATION

Clearance from the IRB of Emory University was sought before data analysis could start. This thesis study would not be directly involved in the collection of data from the research subjects but used data already collected and under the custody of CDC in Atlanta. The author of this thesis has no access to the names of the subjects but was provided access to questionnaires which were only identifiable by codes of the clients. Principle investigators in the field investigation were not directly involved in the analysis of the thesis project but were consulted from time to time for clarification.

3.6.1 Ethical Clearance and Review Board Approval

The protocol for the study was developed with the help of experts from CDC including all data collection tools and consent form. The study was declared non-research by the Ethical Review Board at the Centers for Disease Control and Prevention (CDC). The author of this thesis was granted permission to use data collected during nodding syndrome investigation by the Centers for Disease Control and Prevention (CDC), see **appendix F**. The Emory Institutional Review Board (IRB) committee categorized this thesis as not directly involved with subjects hence did not require formal IRB approval process. This thesis study nonetheless sought to maintain ethical rigor by ensuring that participation in this study was voluntary, due respect was accorded to participants, informed consent was obtained, confidentiality maintained and scientific honesty, as outlined by Babbie and Mouton, 2001 *(45)*.

3.6.2 Confidentiality

This study involved analysis of data collected from the study participants. To conceal study subjects' identification only identifier codes were available to the investigator and no attributes of subjects which could easily identify them like names and exact location were used so that participants were not traceable or identifiable after the study was completed. All data obtained were stored in safe and secure location while primary data remained the property of the Centers for Disease Control and Prevention (CDC).

3.6.3 The consent Process

Before analysis of the data collected the investigators ensured that consent process was duly followed during collection of information from the parents or caretakers of the participants. Parents or caretakers provided informed consent based on information provided on all the details, processes and the purpose of the investigation which was to understand the disease better and identify potential etiologic factors and was NOT designed to offer treatment. A thumbprint was used as surrogate written consent if the adult providing consent was unable to provide a written signature. Refer to **Appendix D** for the consent form used.

3.7 ACTIVITIES TIMELINE

This thesis project analyzed and drew conclusion/recommendations from data collected during Nodding Syndrome cross-sectional survey conducted in South Sudan in May/June 2011. Timeline for activities is as outlined below:

Activity	Period October 2011 – April 2012																											
	Oct				Nov				Dec				Jan				Feb				Mar				Apr			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Proposal writing and submitting																												
Making Corrections and re-submitting for appro																												
Data entry and analysis																												
Writing and Submitting Draft Thesis																												
Making corrections and re-submitting for examination and Presentation																												

3.8 SCOPE AND LIMITATIONS OF THE STUDY

The participants to this study were drawn from 2 out of 10 Counties in Western Equatoria State of South Sudan. The State of Western Equatoria has a total of 10 counties of which 5 had anecdotal reports of nodding syndrome cases.

3.8.1 Conceptual and Time scope

This study examined the relationship between nodding syndrome and nutritional status of children affected with nodding syndrome.

The span of this study was planned to be seven months from start to end (October 2011 – April 2012) and was to cover available information on nodding syndrome dating as far back as the year 2000 in South Sudan.

3.8.2 Limitations of the study:

1. This was a cross-sectional study which sampled the population at a particular point in time, did not therefore allow for the study of the trend of nodding syndrome.
2. Insecurity in nodding syndrome affected counties of the State did not permit selection and inclusion of nodding syndrome cases from insecure counties in the study.
3. Cases selected into the study were based on the sensitivity of the case definition developed which could have miss other cases since this was not confirmed by a laboratory test.
4. Controls were selected from the same village hence were possibly exposed to nodding condition being investigated but not affected, yet, by it.

3.9 RESULTS

3.9.1 Measurements

In order to assess the growth of children affected by nodding syndrome anthropometric measurements were taken to determine their nutritional status. Anthropometry is the measurement of body parameters like height (or length for children who are below two years of age), weight and mid-upper arm circumference including age and sex. When anthropometric measurements are combined with each other or other data valuable indices which can be used to classify nutrition status are generated.

In this study the growth of children affected by nodding syndrome is assessed using anthropometric indices, namely:

- Weight-for-height (WFH) referred to as BMI-for-age since participants were children <18 years, it was used to classify wasting.
- Height-for-age (HFA) to determine degree of chronic malnutrition as known as stunting.
- Weight-for-age to measure the degree of underweight/overweight.

These indices were standardized by converting to z-scores which are deviations from the mean/median. According to the WHO 2007 reference values, undernutrition is classified as severe if z-score is <-3, moderate if z-score is >-3 but <=-2, and normal if z-z-score is >-2.

3.9.1 Type of source population of Nodding Syndrome cases

Of all the participants (both NS cases and their controls) enrolled in this study, 19 (25%) were selected from an internally displaced people's camp (IDP) while the remaining 57 (75.0%) were children who resided with their families in villages which are not IDP locations.

Table 01: Distribution by location of the Nodding Syndrome cases and controls. Data from investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (N=76)**

Status	From Internally displaced camp (IDP)		Total
	Yes	No	
Case	9 (23.7%)	29 (76.3%)	**38**
Control	10 (26.3%	28 (73.7%)	**38**
	19 (25.0%)	**57 (75.0%)**	**76**

** Source: South Sudan MoH/CDC NS investigation data, May/June 2011

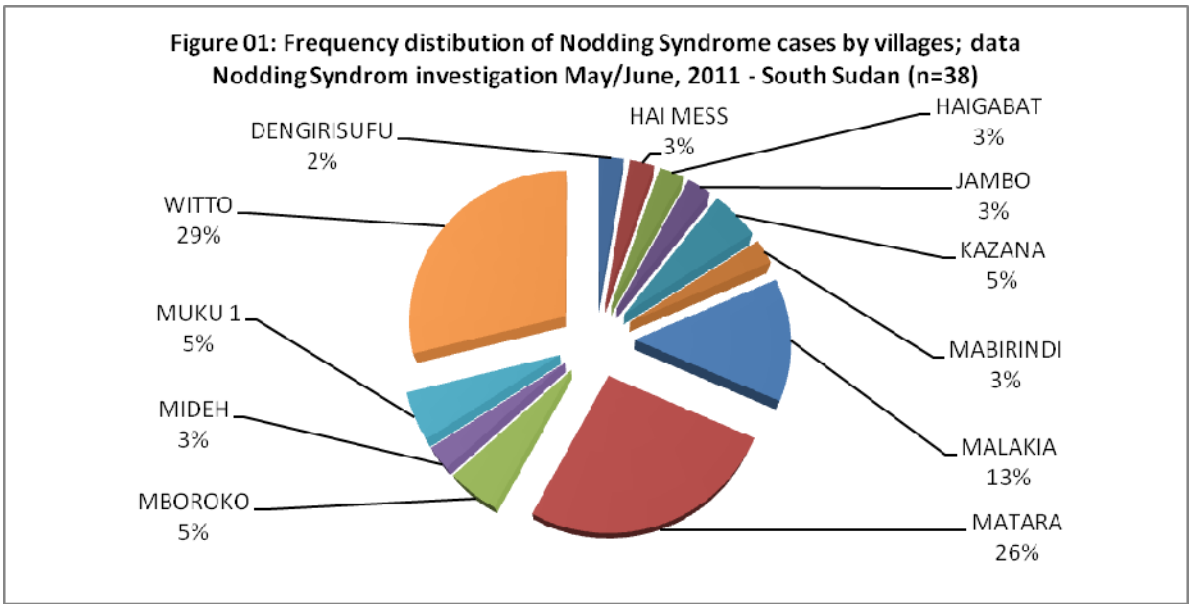
P=0.79

From the analysis in **table 01** above, there is no meaningful difference (p=0.79) in the prevalence of nodding syndrome cases among children selected from the IDP camp and those from non-IDP village locations.

3.9.2 Location of Nodding syndrome cases (n=38)

Figure 01 below shows the distribution of nodding syndrome cases enrolled in the investigation in Maridi and Mundri counties of South Sudan. Twenty-nine percent of nodding syndrome cases in Mundri East county were recorded from Witto IDP village. In Maridi county majority of the cases (26% of the 38 cases) were from Matara village. In a survey of nodding syndrome cases conducted in 2010 by Lagu et

al. they noted high number of nodding syndrome cases in Witto village which is a camp for internally displaced people (IDP).



3.9.3 Anthropometry

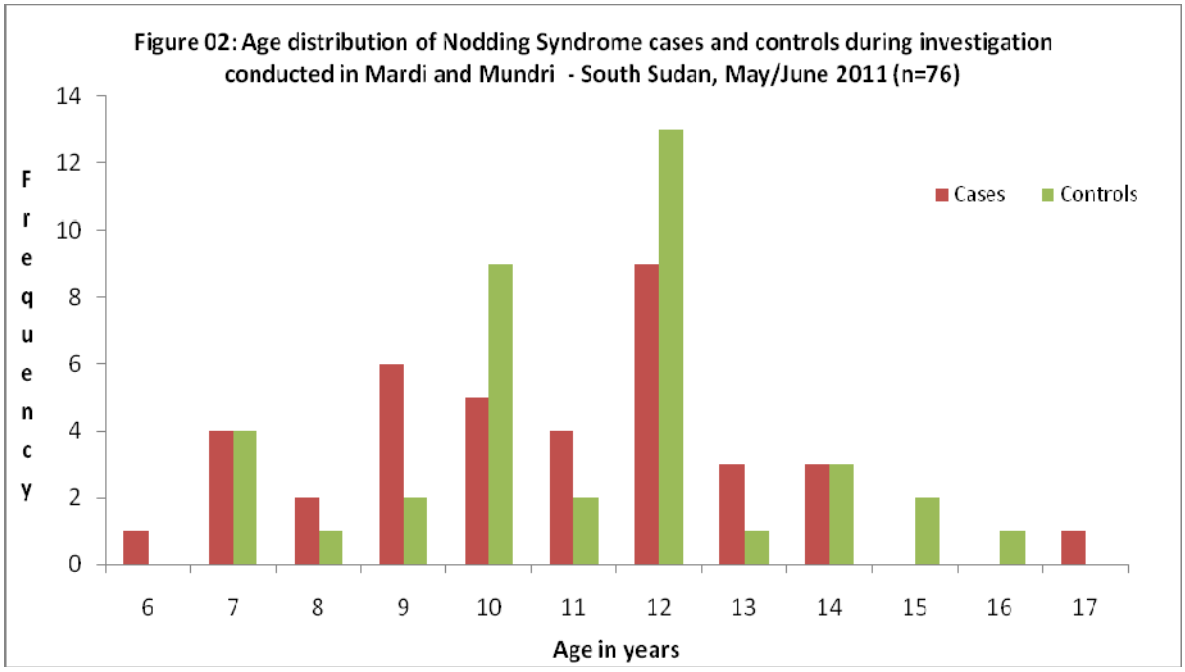
3.9.3.1 Sex of participants

Of the 38 nodding syndrome cases enrolled for the study from the counties of Maridi and Mundri 52.6% (20/38) were males while 47.4% (18/38) were females. This is a statistically non significant (p=0.65) variation between male and female children affected by nodding syndrome from the study sample. No comparison is made of the ages of nodding syndrome and their controls because during the case-control study nodding syndrome cases were required to be less than 15 years and should have had nodding disease for 3 years or less while in the case-series arm of the study there was no restriction on the ages of the cases of nodding syndrome.

Controls were required to be within 2 years of the cases and living within the same village of IDP location.

The mean age of children with nodding syndrome enrolled into the study was 10.6 years (median age 11 years) while the mean age of paired controls in the same study was 11.1 years (median age 12 years) which is within planned matched criteria of the study (controls were selected when within 2 years of age of the matched case).

In **figure 02** below the frequency distribution of ages of children affected by nodding syndrome enrolled in the study is shown.



In figure 03 below the percentile age distribution of cases and controls shows that the age of nodding syndrome cases and controls enrolled in the study were not different.

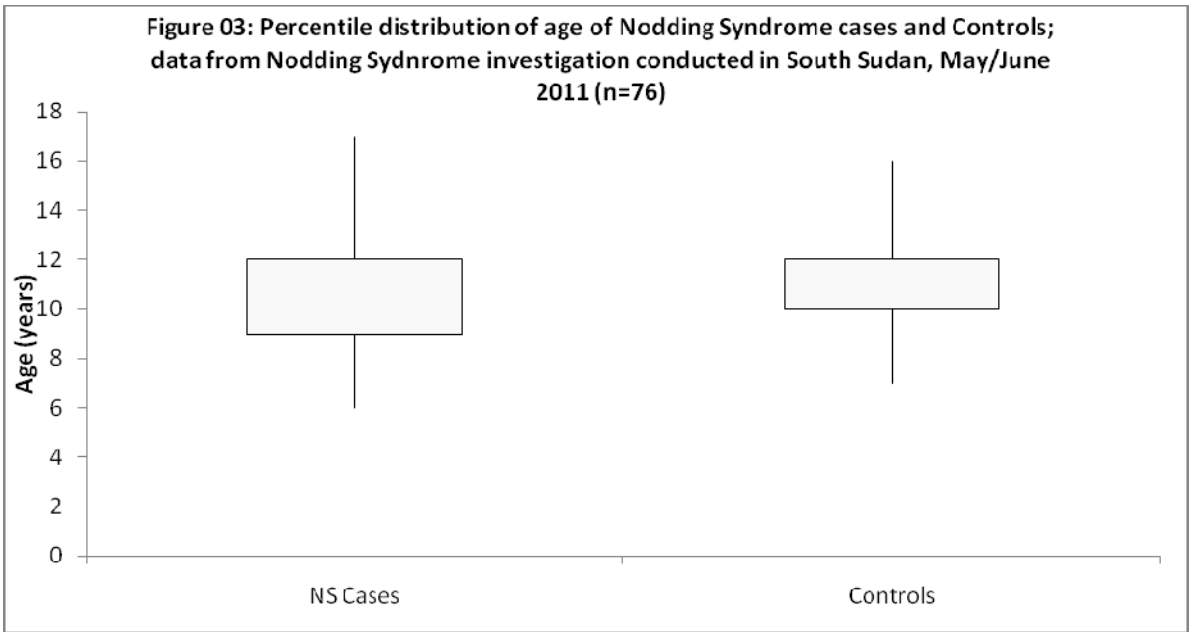
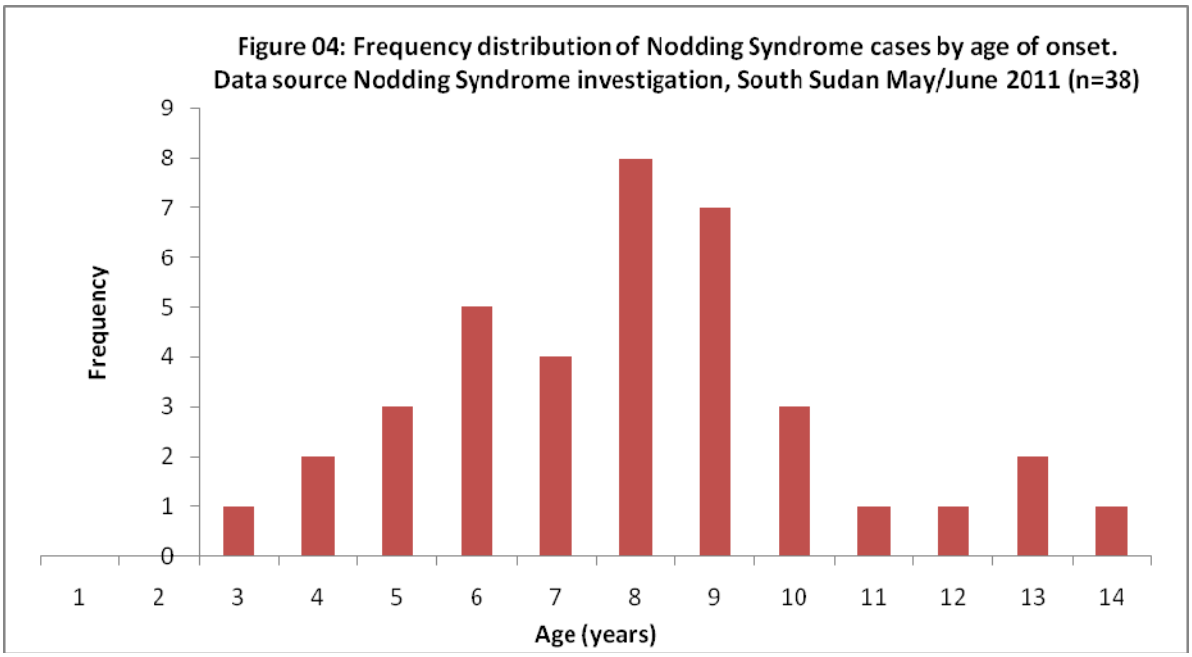


Figure 04 below shows the distribution of age at onset of nodding syndrome. The average age at onset of nodding syndrome was 8 years (±2.54) among the 38 nodding syndrome cases enrolled in the study.



In **table 02** below the mean duration of nodding syndrome is compared between male and female cases. Among nodding syndrome cases enrolled in the study, the difference between the mean duration of illness in males and females is not statistically significant (p=0.76). This comparison is important because much as there was restriction in the duration nodding syndrome during selection of cases subsequent analysis shows the males and females had indifferent duration of the condition.

Table 02: Comparing the mean duration (years) of Nodding Syndrome in male and female cases. Data from investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (n=38)

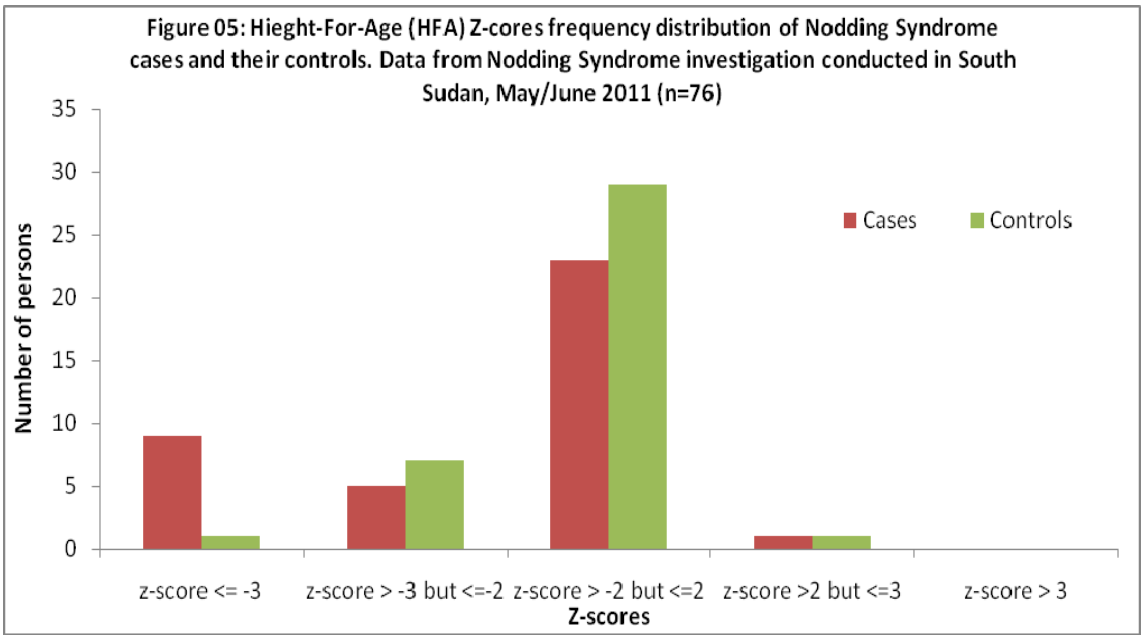
Continuous variable	Female mean duration (SD) n=18	Male mean duration (SD) n=20	Mean duration difference	t-test p-value (two-tailed)
Duration of illness (years)	1.92 (±0.97)	1.82 (±1.04)	0.1	0.76

~~ Data from NS investigation conducted in South Sudan May/June 2010; analyzed in EpiInfo 3.5.3 and openepi

3.9.3.2 Stunting: Height for Age (HFA) index Analysis

In order to assess for stunting in an individual, which is a sign of chronic undernutrition, the index of height-for-age is measured. Data were analyzed to compare the height-for-age (HFA) of cases (n=38) and controls (n=38) enrolled in the study. Reference values for height-for-age z-scores were derived from WHO 2007 reference charts for children 5 to 19 years. The World Health Organization classifies severe stunting (low height for age) as height-for-age z-score < -3, moderate stunting when the z-score > -3 but <=-2, and normal growth when height for age z-score > -2.

Figure 05 below compares categorized z-scores height-for-age (HFA) of all nodding syndrome cases and their controls (unmatched). It is noted that 23.7% of all nodding syndrome cases had height-for-age (HFA) z-scores <-3 meaning were severely stunted while 2.7% of their controls had height-for-age (HFA) z-scores <-3. There is a statistically significant difference in the proportion of severe stunting (HFA z-score <-3) between nodding syndrome cases and their controls (Fisher's exact p=0.01), with the odds that a nodding syndrome case had severe stunting being 9 times (95% CI: 1.38, 95.88) the odds that a control had severe stunting.



3.9.3.3 Comparison of Nodding Syndrome cases and controls by Height-For-Age (HFA) z-scores

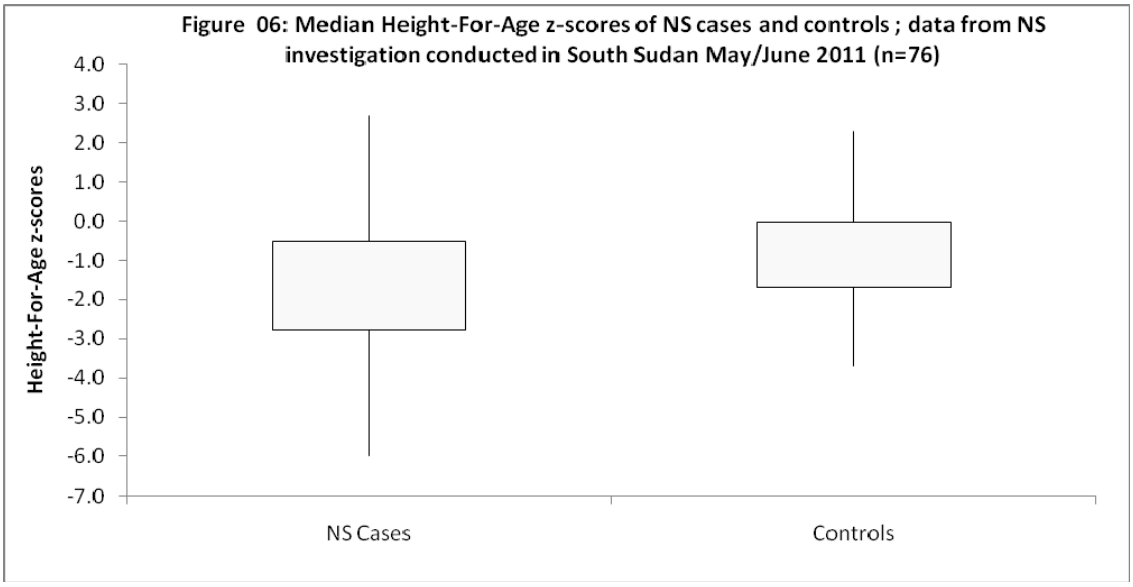
In table 03 below, the mean height-for-age z-scores of nodding syndrome cases and their control friends are compared (unmatched). Analysis indicates that the difference between the height-for-age (HFA) z-scores of nodding syndrome cases and their controls is statistically significant (p=0.02), the level of stunting in

nodding syndrome cases and controls is different – nodding syndrome cases are more stunted.

Table 03: Unmatched Comparison of the mean Height-For-Age (HFA) z-scores of Nodding Syndrome cases and their controls. Data from investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (n=76)

Continuous variable	Control mean HFA z-score (SD) n=38	NS cases mean HFA z-score (SD) n=38	HFA mean z-scores difference	t-test p-value (two-tailed)
HFA z-scores	-0.79 (+1.32)	-1.71 (+1.90)	0.92	0.02

In **figure 06** below the median height-for-age z-scores of nodding syndrome cases and their controls is further illustrated. The median height-for-age z-scores of nodding syndrome cases and controls are different.



3.9.3.4 Matched analysis of Severe Stunting (height-for-age z-score <-3) in Nodding Syndrome cases and their controls.

In **table 04** below a matched comparison of nodding syndrome cases and their controls is made for severe stunting (height-for-age z-scores <-3) using the McNemar's analysis in openepi software (zero cells are compensated for by adding 0.5 to every cell).

Table 04: Matched analysis of Nodding Syndrome cases and their controls by severe stunting (Height-For-Age z-score <-3); data from Nodding Syndrome investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (n=38 pairs)**

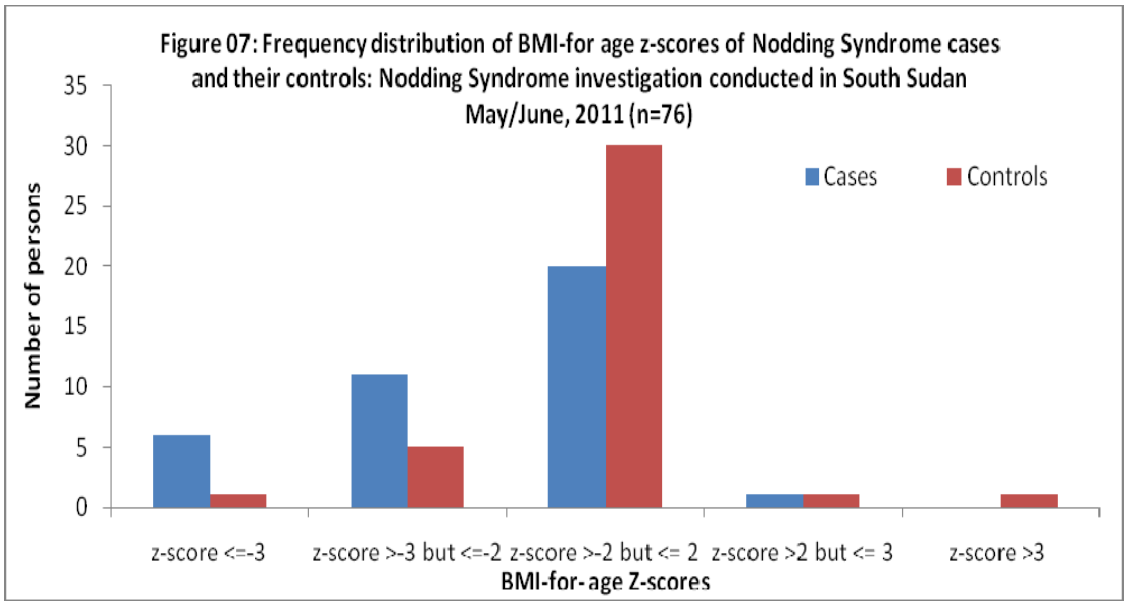
Case	Controls		Total
	HFA z-score <-3	**HFA z-score >-3**	
HFA z-score <-3	0	9	**9**
HFA z-score >-3	1	28	**29**
	1	**37**	**38**

** Source: South Sudan MoH/CDC NS investigation data, May/June 2011: Used EpiInfo 3.5.3 and Openepi

From **table 04** above the odds of severe stunting is 9 times in nodding syndrome cases compared to their matched controls. The difference between severe wasting in nodding syndrome cases and their matched controls is statistically significant (p=0.03). This finding is in line with the statistical conclusion in item **3.9.3.3** above, indicating difference in the height-for-age z-scores of nodding syndrome cases and their controls hence different stunting levels.

3.9.4 Wasting: Body-Mass-Index for age (BMI-for Age) analysis

In order to assess for wasting in nodding syndrome cases and their controls their weight-for-Height (WFH) measurement index also known as Body Mass Index (BMI) was taken. In this study BMI-for-age index will be used because it is age specific for children and the amount of body fat differs between boys and girls. All children enrolled in this study were over the age of 5 years but below 19 years of age, the WHO 2007 BMI-for-age reference charts were therefore used to determine the trend of wasting. Sixteen percent of all nodding syndrome cases (6/38) had BMI-for-age z-scores <-3 while 2.6% (1/38) of the controls had BMI-for-age z-score <-3 (OR=6.9, Fisher's exact p=0.11) indicating a statistically non-significant difference in severe wasting between nodding syndrome cases and their controls, this is also shown in **figure 07** below.



3.9.4.1 Unmatched Comparison of Wasting (BMI-for-Age z-scores) of Nodding Syndrome cases and their controls

In **table 05** below, the means of BMI-for-age z-scores for all nodding syndrome cases and their controls are compared.

Table 05: Comparing the BMI z-scores of Nodding Syndrome cases and their controls. Data from investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (N=76)

Continuous variable	Control mean BMI-for-age z-scores (SD) n=38	NS cases mean BMI-for-age z-scores (SD) n=38	Mean BMI-for age z-scores difference	t-test p-value (two-tailed)
BMI-for age z-scores	-0.99 (±1.53)	-1.69 (±1.71)	0.70	0.06

@ Analyzed in EpiInfo version 3.5.3 and Openepi software

The difference between the BMI-for-age z-scores of nodding syndrome cases and their controls (unmatched) is not statistically significant (p=0.06). This is not in contrast to the finding in **figure 07** above where it was noted that there is no difference in the prevalence of wasting between children affected by nodding syndrome and their controls.

3.9.4.2 Matched analysis of Nodding Syndrome cases and their paired controls for severe wasting (BMI-for-age z-score <-3)

In **table 06** below, matched data from nodding syndrome cases and their controls were analyzed for severe wasting based on their BMI-for-age compared to WHO 2007 standard reference values.

Table 06: Matched analysis of Nodding Syndrome cases and their controls by severe wasting (BMI-for-age z-score <-3); data from Nodding Syndrome investigation conducted in South Sudan May/June 2011 by MoH/RoSS and CDC (n=38 pairs)**

Case	Controls		Total
	BMI-for-age z-score <-3	**BMI-for-age z-score >-3**	
BMI-for-age z-score <-3	0	6	**6**
BMI-for-age z-score >-3	1	31	**32**
	1	**38**	**38**
Matched OR = 6 (95% CI: 0.72, 49.83) and p=0.06			

** Source: South Sudan MoH/CDC NS investigation data, May/June 2011: Used EpiInfo 3.5.3 and Openepi

Based on the finding in **table 06** above the odds of severe wasting (BMI-for-age z-score <-3) among nodding syndrome cases is 6 times (95% CI: 0.72, 49.83) the odds of severe wasting in the controls. The difference between the risk of severe wasting in nodding syndrome cases and their matched controls is not statistically significant (p=0.06).

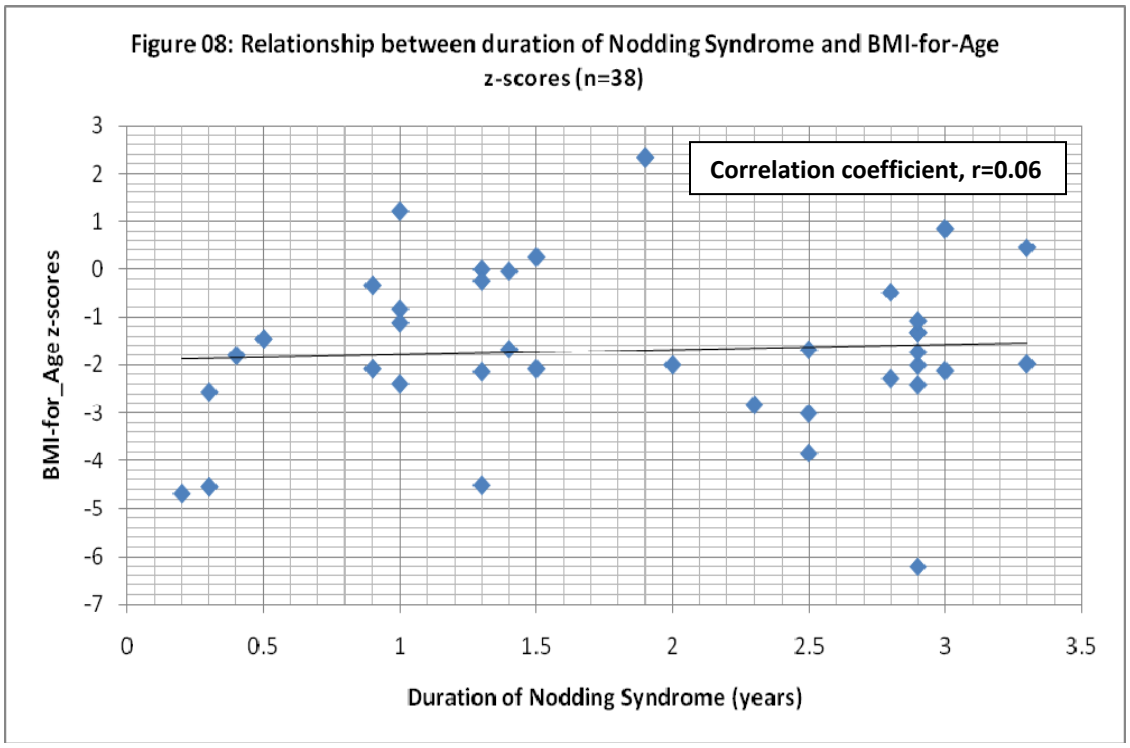
3.9.5 Correlation between Duration of Nodding Syndrome, Stunting and Wasting

During the nodding syndrome investigation conducted in South Sudan 38 nodding syndrome cases were enrolled in the case-control arm of the study while 18 additional cases were enrolled in the case-series arm of the same study. The cases in the case-series arm were enrolled for detailed description of the condition. During the selection of cases into the case-control arm of the study the inclusion criteria restricted eligible cases to be below 18 years of age and should have had nodding syndrome for an approximate duration of not more than 3 years. In the case-series arm there was no restriction in the age of enrollment and duration of illness. Nodding syndrome cases in the case-control arm of the study were therefore relatively younger (average age 10.6 years, ±2.53 SD) than those in the case-series (average age 14.9 years, ±2.68 SD) and have had the condition for a shorter period (average duration 1.8 years, ± 0.72 SD) compared to those in the case-series arm (4.9 years, ±1.02 SD).

3.9.5.1 Wasting in Case-Control cases (BMI-for-Age z-scores) and duration of Nodding Syndrome

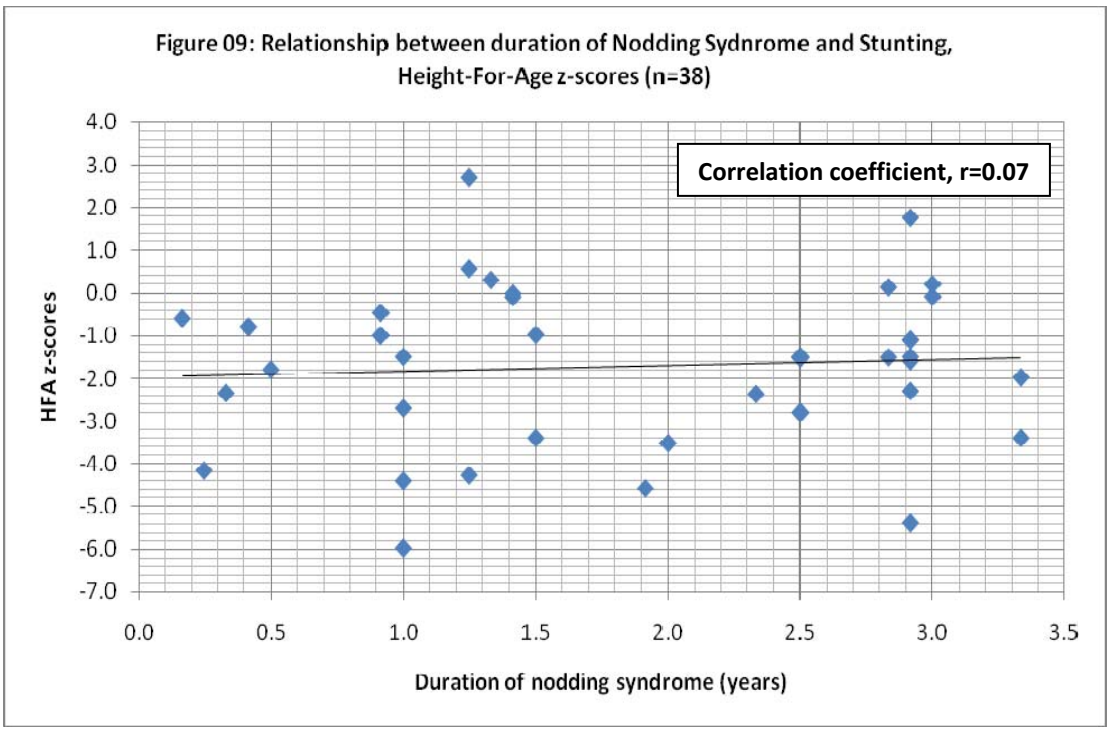
In order to determine the nature of relationship between wasting and the duration of nodding syndrome a correlation analysis as shown in **figure 8** below was made. A positive or negative correlation does not imply causal or effect relationship because the direction of the cause is not known besides there could be a third variable causing the observed effect. It is noted that the relationship between the

duration of nodding syndrome in the cases and wasting does not generate a strong correlation (r=0.06).



3.9.5.2 Stunting (height-for-age z-scores) and duration of Nodding Syndrome

In **figure 09** below the relationship between stunting in nodding syndrome cases and duration of the condition is positively related but weakly (r=0.07).



3.9.5.3 Combined (Nodding Syndrome cases) Analysis of the relationship between Stunting (Height-For-Age z-scores) and durtaion of Nodding Syndrome (n=50)

In **figure 10** below the extent of stunting (height-for-age) is related to the duration of nodding syndrome when nodding syndrome cases in the case-control and case-series arms of the study are combined in a single analysis.(n=50).

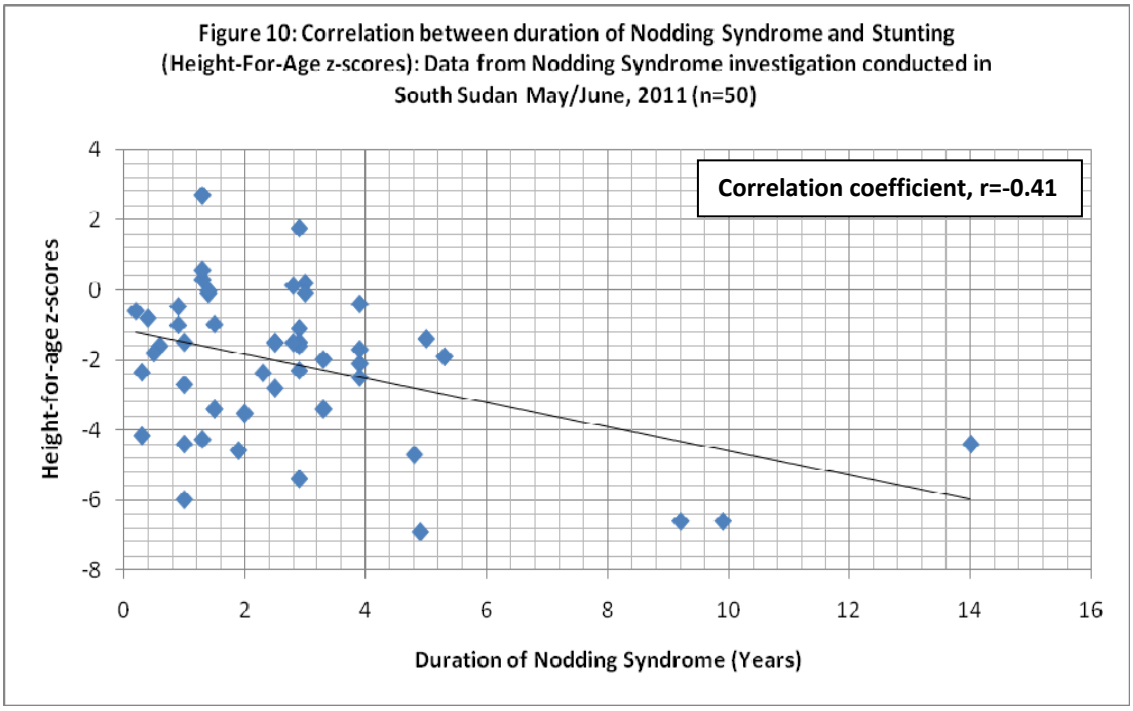
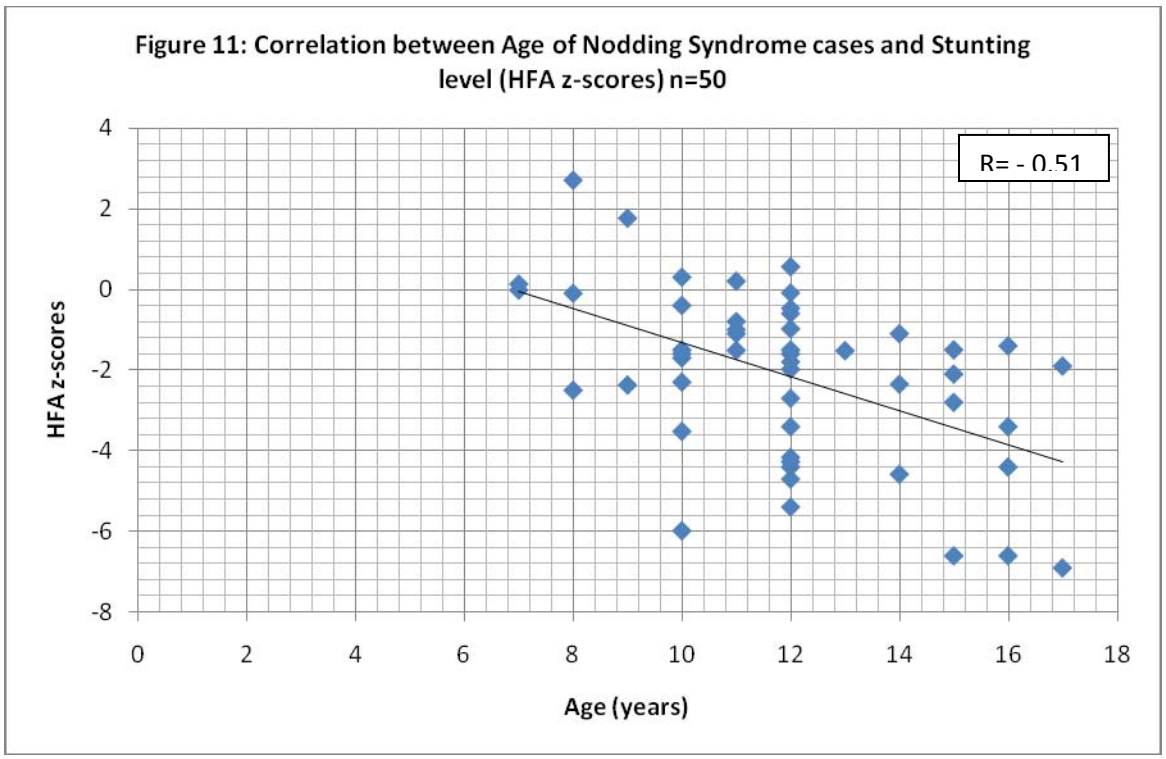


Figure 10 above shows that the longer the duration of nodding syndrome in a child the higher the chances of stunting (low height-for-age index). The correlation between durtaion of nodding syndrome and stunting is inversely proportional and strong (r=0.41). This means that as the duration of nodding syndrome increases in a patient the level of stunting as measured by HFA z-score decreases.

3.9.5.4 Analysis of the relationship between Stunting (Height-For-Age z-scores) and Age of Nodding Syndrome (n=50)

In **figure 11** below the correlation between stunting and age of nodding syndrome cases is explored. The risk of stunting increases with incresing age of nodding syndrome cases, there is a strong negative correlation (r=-0.51) meaning as the age of nodding syndrome cases advances their height-for-age z-scores decreases (severity of stunting increases).



3.10 HISTORY OF CHILD GOING HUNGRY

Hunger is a direct cause of undernutrition in children and in the presence of an illness it retards growth as shown by nutritional status of those affected. In this study comparison is made between children who were reported to have gone hungry between nodding syndrome cases (n=38) and their controls (n=38) in an unmatched analysis. Twenty-four percent of children with nodding syndrome and 7.9% of their controls were reported to have gone hungry at least once in their lifetime by the parents, guardians or caretakers.

Table 07 below shows a crude analysis of all the participants enrolled in the investigation based on their exposure or no exposure to hunger before, during or after development of nodding syndrome.

Table 07: Unmatched Comparison of history of going hungry in Children among Nodding Syndrome cases and their controls in Mundri and Maridi counties. Data from Nodding Syndrome case-control investigation conducted in South Sudan May/June 2011(n=76).

Category	History of going hungry		Total
	Yes	No	
Case	9	29	38
Control	3	35	38
	12	64	76
OR: 3.62 (95% Confidence interval: 0.89, 14.63); Fisher's exact p=0.11[&]			

& At least one expected value (row total *column total/grand total) is <5

There is no meaningful difference (Fisher's exact p=0.11) in the history of going hungry between nodding syndrome cases and their controls; nodding syndrome cases have 3.62 times odds of being exposed to hunger compared to controls in Mundri and Maridi counties.

The relationship is further analyzed upon stratification by sex to check if there was differential in exposure to hunger based on sex of the child. This analysis is done to check if underlying cultural or social factors led to differential exposure of either male or female children to hunger.

In **table 08** below a stratified analysis of the crude **table 07** above is presented to check if sex of a child confounds the relationship between history of going hungry and nodding syndrome.

Table 08: Comparing history of going hungry among Nodding Syndrome cases and their controls in Mundri and Maridi stratified by sex of participants. Data from Nodding Syndrome case control investigation conducted in South Sudan May/June 2011(n=76).

Males (n=38)				Females (n=38)			
Category	**History of going hungry**		**Total**	**Category**	**History of going hungry**		**Total**
	Yes	**No**			**Yes**	**No**	
Case	4	16	20	**Case**	5	13	18
Control	2	16	18	**Control**	1	19	20
	6	32	38		6	32	38
OR:2.00 (95% Cl: 0.32, 18.51) Fisher's exact p=0.77				OR:7.31 (95% Cl: 0.76, 70.02) Fisher's exact p=0.14			

Crude OR: 3.62 (95% CI: 0.89, 14.63); Strata specific OR, Males: 2.00 (95% Cl: 0.32, 18.51) and Females, OR: 7.31 (95% Cl: 0.76, 70.02).

Analysis:

Using Breslow-Day analysis the Chi-square is **0.76** while the p-value is **0.38** which is greater than 0.05 indicating no interaction between sex and history of going hungry in nodding syndrome cases and controls, therefore the adjusted Odds ratio, **MH Adjusted OR 3.53 (95% CI: 0.89, 14.08).**

Stratifying the relationship between history of going hungry and nodding syndrome by sex in nodding syndrome cases and controls in Mundri and Maridi counties of WES does not produce a significant difference across strata (Chi-square is **0.76** while the p-value is **0.38**). Therefore, at 5% significance level the sex of a

participant (in both cases and controls) does not modify the relationship between history of going hungry and nodding syndrome status.

Comparing the MH adjusted OR = **3.53 (0.89, 14.08)** to the crude OR of **3.62** in the absence of interaction, produces an adjusted OR that is not meaningfully different from the crude OR when using a ±10% difference as the definition of meaningful. The adjusted OR lies within ±10% bounds of the crude **OR (3.26, 3.98).** Sex therefore neither confounds nor modifies the relationship between history of exposure to hunger and status of nodding syndrome in both cases and controls enrolled in the investigation.

Therefore, with reference to the crude data as shown in **table 07** above, at 5% significance level there is no meaningful difference (Fisher's exact p=0.11) in the history of going hungry between nodding syndrome cases and their controls enrolled in the study; nodding syndrome cases have 3.62 times odds of history of going hungry compared to controls in Mundri and Maridi counties.

CHAPTER 4

DISCUSSION, RECOMMENDATIONS AND CONCLUSION

4.0 INTRODUCTION

In this chapter nodding syndrome study results are discussed and to the extent possible references are made to relevant studies conducted during the last 10 years, preferably in the context of South Sudan or sub-Saharan Africa. In order to assess the growth and development of children affected by nodding syndrome their nutritional status (stunting, wasting and underweight) was determined by measurement of anthropometric indices (height-for-age, weight-for-age and BMI-for-age) which were compared to those of their control friends. Nodding syndrome cases and controls were recruited in this study based on inclusion and exclusion criteria defined before the study but informed by on-going data collection and analysis on the condition in South Sudan. Nodding syndrome cases were selected into the case-control arm of the study if they were under 18 years of age and have had the condition for not more than 3 years. On the other hand nodding syndrome cases (n=12) enrolled into a concurrent case-series of the same study were not restricted by age and duration of illness. Control friends were required to be within 2 years of their matching case.

4.1 DISCUSSION

4.1.1 Anthropometric information

Undernutrition has been recognized in other neurological diseases like cerebral palsy, epilepsy in both adults and children *(46)*. The importance of malnutrition in

patients with neurological conditions is related to the possible influence of nutritional status in the long term prognosis, as well as to the predisposition to infections *(47)*. In this study nutritional status of nodding syndrome cases was assessed using anthropometric measurements to determine the growth status of children affected by nodding syndrome considered a neurological, seizure-like condition in Western Equatoria State (WES) of South Sudan.

4.1.1.1 Gender of Participants (Male and Female)

The mean age of nodding syndrome cases in this study was 10.6 years (± 2.4) while their mean age at onset of nodding syndrome among the cases was 8 years (±2.5) and the average duration (from onset to the time of the study) of the condition in the cases was 1.8 years (±1.04), this was expected because nodding syndrome cases enrolled in the case-control arm of the study were restricted to under 15 years of age and should have had the condition for not more than 3 years. The average age of nodding syndrome cases found in this study is not different from what was found in a clinical descriptive study of 62 nodding syndrome cases conducted in southern Tanzania *(48)*. In a study conducted in Kenya it showed that the highest age-specific incidence of epileptic seizures occurs between birth and 9 years of age *(49)*. The average age of onset of nodding syndrome in the cases enrolled for the investigation falls within the age group noted with increased incidence of epileptic seizures in other countries like Uganda, Kenya and Tanzania.

4.1.1.2 Stunting: (Height-for-Age) index

Height-for-age (HFA) is a measure of linear growth in an individual, failure to reach optimal linear growth is reflected in low height-for-age. Severe stunting is defined by height-for-age z-score less than -3 and at the population level a stunting rate between 30 and 39.9% is considered "high" while above 40% is considered "very high" *(50)*.Failure to attain optimum height-for-age could be due to ill-health, inadequate nutrient intake, genetic predisposition, growth/sexual hormones deficiency also known as hypophisal dwarfism. The analysis of height-for-age index of nodding syndrome cases in comparison to their controls indicates that nodding syndrome cases have a higher chance of severe stunting (height-for-age z-score <-3) compared to their controls (OR 9.9), a statistically significant finding (Fisher's exact p=0.01). The same trend of higher rates of severe stunting in nodding syndrome cases than their controls is observed when a paired analysis is conducted. According to the report of the South Sudan Household Survey (SSHHS: 2006), (*51*) the prevalence of severe stunting in Western Equatoria State (WES) for children below the age of 5 years was 10.7%. The finding in this study therefore indicates that the rate of severe stunting (height-for-age z-score <-3) in nodding syndrome cases is over and above the trend in the general population. Referring to the average duration of nodding syndrome (from onset to the time of study) in cases being 1.8 years; nodding syndrome is considered a chronic ill-health status that is likely to increase demand for nutrients which the body of an affected child is not able to provide due to reduced intake and prevalent poverty. This argument is further supported by strong negative correlation (r=-0.41) between the duration of illness (nodding syndrome) and stunting in addition to strong negative (r= -0.51)

correlation between age of nodding syndrome cases and stunting when all nodding syndrome cases from the case-control and case-series arms of this study (n=50) were combined and analyzed together. Since the head nodding in nodding syndrome cases is frequently described as a neurological and seizure-like condition triggered by the presence of food it is possible that caretakers and parents abstain from giving children with nodding syndrome food for fear of triggering an episode of nodding and subsequently seizures. Beyond the trend of stunting observed in nodding syndrome cases which could be as a result of ill-health, reduced intake and/or community practices; nodding syndrome being a neurological condition could be affecting the production of growth and development hormone in the brain which in turn affects the development of secondary sexual characteristics, skeletal deformities and dental caries. This is further supported by the analysis of age, duration of nodding syndrome cases and height-for-age z-scores (stunting) which shows increasing tendency of stunting with increasing duration and age of those affected by the condition. In a study conducted in Uganda a disease called "Nakalanga Syndrome" comprising epilepsy, stunting and mental retardation has been associated with severe stunting and low levels of growth hormone in the persons affected; during its investigation in Western Uganda 70% of the 231 young adults screened were found to be stunted *(52)*.

Consistently stunting has been linked to children with mental retardation and neurological deficits *(53)*, in addition a relationship between feeding problems and growth retardation has been reported in children with mental retardation and cerebral palsy *(54)*. Succinct evidence on how, and to what extent various

neurological conditions and feeding problems may influence growth in different groups of children with cognitive impairment is, however, scarce.

4.1.1.3 Wasting: BMI-for-Age index

Weight-for-Height (WFH) is a body measurement index that determines the degree of wasting considered undernutrition in both children and adults *(55)*. In this study BMI-for-age index was used because it is age specific for children and the amount of body fat changes with age. The prevalence of severe wasting (BMI-for-age z-score <-3) among nodding syndrome cases in this study was determined to be 16% while in their controls was 2.6%. Paired analysis of nodding syndrome cases and their controls also indicated no difference (p=0.06) in the prevalence of severe wasting between cases and controls. Comparing these findings to the Southern Sudan Household Survey (2006: indicator 66) which found the prevalence of severe wasting (WFH z-score <-3) in children under five years of age to be 4.0% in Western Equatoria State, the rate of severe wasting in nodding syndrome cases was twice the estimated population rate. Studies have shown that neurological impairment is considered the best predictor of nutritional status especially if it occurs rapidly and associated with feeding impairment which may lead to acute nutritional deficiency associated with wasting *(56)*.

A study conducted in Zambia found that children with subtle neurological deficits had recurrent acute undernutrition episodes due to: feeding difficulties, co-existing infections, differentials in feeding practices compared to healthy children in the family and stigma associated with children who are mentally challenged *(57)*.

Severe wasting in nodding syndrome cases could be due to inadequate food intake, ill-health (nodding syndrome) or/and caretakers abstaining from feeding children for fear of triggering nodding episodes.

4.1.2 Relationship between Stunting, Wasting and duration of Nodding Syndrome

During a nodding syndrome study conducted in South Sudan by Winkler et al. 2008 *(58),* it was noted that 40% of patients had short stature (although the degree of short stature was not quantified) indicating the association between nodding syndrome, growth and development. In this study among the thirty-eight nodding syndrome cases enrolled in the case-control arm there was weak correlation (r=0.06) between the duration of nodding syndrome and stunting, when only the patients recruited into the case control were considered. A stronger correlation (r= -0.41) was observed between the duration of nodding syndrome and stunting when all nodding syndrome cases were combined and analyzed together compared to that observed in case-control nodding syndrome cases who have had the condition for a relatively shorter duration. Notwithstanding the fact that the sample size in this study was small this correlation between stunting and duration of nodding syndrome indicates that the risk of stunting (manifested by decreasing height-for-age z-scores) in nodding syndrome cases increases with increasing duration of the disease.

A weak correlation (r=0.08) was found between the duration of nodding syndrome and wasting among nodding syndrome cases in the case-control arm of the study. The average duration of nodding syndrome cases in the case-control arm of the

study was 1.8 years while the average duration of nodding syndrome in all nodding syndrome cases (case series and case-control combined) was 4.5 years.

Further comparison of height-for-age and BMI-for-age z-scores of nodding syndrome cases indicate that the risk of stunting (height-for-age z-scores) and wasting (BMI-for-age z-scores) increases with increasing duration of the condition. This finding supports the evidence in literature that the chronic nature of neurological disorders in children is associated with cognitive impairment, growth retardation and severe malnutrition and seems to suggest that nodding syndrome may be the cause of malnutrition in children affected *(59)*.

4.1.3 History of Going Hungry

In this study nodding syndrome cases and controls were compared on the history of going hungry. There was no statistical difference in the history of going hungry between male and female nodding syndrome cases (Fisher's exact p = 0.11). On stratifying by sex between nodding syndrome cases and controls for history of going hungry, there was no difference in the history of going hungry between nodding syndrome cases and their controls. This analysis was important to determine if there were differential feeding practices between males and females in the communities due to prevailing cultural practices which could include food taboos and socioeconomic conditions which placed one sex group at a better position compared to another in terms of access to food and feeding. Besides this analysis also helped check if nodding syndrome cases were allowed to go hungry because parents/caretakers withheld food from children affected for fear of triggering head nodding episodes.

4.2 LIMITATIONS OF THE STUDY

The nodding syndrome investigation conducted in May/June, 2011 had limitations. Below is a snapshot of the limitations which have been taken into consideration during analysis and discussion of the study results.

The study population was children with nodding syndrome in Western Equatoria State (WES) of South Sudan. Children selected into the study were supposed to be from a cross-section of nodding syndrome cases seen in Mundri, Mvolo and Maridi counties based on outlined inclusion and exclusion criteria. The study team however could not go to Mvolo county due to insecurity in the area so children with nodding syndrome in this county are not represented in this study.

During the study caretakers or parents of children with nodding syndrome and their controls were asked about the history of the child going hungry. The answers to these questions could have been either over or under reported due to recall bias.

Nodding syndrome is commonly described as a seizure-like neurological condition which could affect the growth and development pattern of children affected. During this study no data were collected on the sexual development of the children affected especially those at the age of puberty and beyond. This would have been important in determining whether nodding syndrome affected growth and development and if it did were the changes due to nutritional or/and hormonal deficits.

Selection of nodding syndrome cases into the study was not randomly done, it was based on screening of the suspected cases using outlined inclusion and exclusion criteria (case definition) appraised by in-country surveillance, ministry of health and WHO team of technical experts.

Children enrolled into the nodding syndrome investigation were from two different settings; thirteen children with nodding syndrome were selected from Witto village which is a residential place for internally displaced persons (IDP) who had access to humanitarian food assistance while the rest of the twenty-five cases in the case-control arm of the study were from non-IDP locations around Witto and Maridi county and were not provided food assistance.

4.3 RECOMMENDATIONS

The analysis of the results of this study indicates that among the 50 children with nodding syndrome enrolled in study (both in the case control and case series arms):

- Severe stunting is more frequent in nodding syndrome cases than their controls.
- There is no statistical difference in the prevalence of wasting and underweight between nodding syndrome cases and their controls.
- Nodding syndrome cases that have had the condition for a longer duration are more stunted than nodding syndrome cases that have had the condition for a shorter duration.
- There is no difference in the history of going hungry between nodding syndrome cases and their controls; further comparison of history of going hungry by sex (male and female) did not indicate any difference between nodding syndrome cases and their controls.

The Millennium development summit in 2000 established seven goals for the prevention of malnutrition, which included: universal primary education, reduced maternal and child mortality rates, empowerment of women, prevention and

management of HIV/AIDS, malaria and other infectious diseases including tuberculosis, protection of the environment and development of sustainable partnerships *(60)*. In order to reduce child mortality as outlined in the Millennium Development Goal number – four *(61)*, intense nutrition action is needed in terms of prevention, early detection and management of children with malnutrition (undernutrition). Timely detection and management of undernutrition, including in nodding syndrome children, is critical not only for the welfare of children but also for the socioeconomic development of nations and communities *(62)*.

There are many contributing factors to the cause of malnutrition which necessitates intersectoral and all-inclusive programs to address the issue *(63b)*. In order to provide appropriate recommendations given the findings of this study, an understanding of the immediate, underlying and basic factors leading to malnutrition have to be considered and understood. Immediate factors leading to malnutrition in children include: inadequate intake and occurrence of infections and other diseases. The results observed are compatible with a nutritional cause of stunting, as well as with a hormonal etiology. It is important to identify which is the cause of stunting in order to prevent and revert it. While underlying factors include among others: social norms, gender and equity, maternal access to education, health care and household food, and nutrition security *(65b)*. Discovering and assessing the cause and pathophysiology of nodding syndrome is paramount to its control. Meanwhile, we need to ensure that every effort is made to improve the lifes of children affected by nodding syndrome, to advocate for safe living environment for the children affected, and to prevent malnutrition and unnecessary deaths.

4.3.1 Immediate and Intermediate Recommendations

Co-infection with diseases like malaria, respiratory tract infections and diarrhea increase the risk of children affected by nodding syndrome in becoming malnourished. Timely treatment of such infections or infestations in children affected by nodding syndrome children will help reduce their becoming malnourished and increase their survival. This should however be done in consultation with existing guidelines of managing common childhood conditions in South Sudan.

Nodding syndrome is commonly described as a seizure-like condition; it is possible that head nodding interferes with the frequency of feeding in children affected. If these episodes of head nodding have been confirmed to be seizures-like and interfere with the ability of children affected to feed by a qualified health worker the possibility of administering anti-convulsion drugs should be explored based on existing national guidelines and the results of upcoming treatment trials.

In order to establish sustainable management and follow-up of nodding syndrome cases a surveillance system should be created within the existing system to track, establish the burden and further investigate the condition so that appropriate actions can be taken to improve the lifes of those affected and prevent unnecessary morbidity and mortality. Among on-going activities for parents of nodding syndrome patients may include regular growth monitoring of children affected, psychosocial counseling, and education on how to feed and care for children affected by nodding syndrome.

Based on the ill-health condition of children affected by nodding syndrome; additional food to meet increased body demand will be necessary. Children affected

by nodding syndrome would benefit from targeted nutrient rich supplementary food distribution. This needs to be planned within the framework of the already existing system mindful of the situation that some nodding syndrome cases in IDP villages occasionally receive food rations while those from non-IDP villages do not receive food rations.

In addition to targeted supplementary feeding program children affected by nodding syndrome should be offered micronutrient supplementation to provide for the deficit caused by virtue of the illness and reduced intake given prevalent poverty in the region leading to a family diet which is not diverse in nutrients. Micronutrients for supplementation should include: vitamin A, calcium, iron (depending on clinical assessment), folic acid and vitamin B-complex.

4.3.2 Recommendations to address underlying factors

Several factors influence infant and young child feeding including: socio-cultural beliefs about infant and young child feeding (such as withholding food during illness), traditional healthcare practices, influence of family and friends on the type, quality and frequency of food to be fed to children, stringent food taboos and other commercial pressures *(63)*. Interventions like community education, setting up mother support groups and with-in community screening of children for malnutrition, and a program to explore and address prevailing infant and young child feeding practices should be implemented with the help of community members. These interventions will be opportunities to provide more awareness and education on the care for children with nodding syndrome and also reduce stigma associated with the condition in the communities affected.

Parents and caretakers of children affected by nodding syndrome have and continue to endure enormous psychological trauma given the chronic and debilitating nature of the condition of the children affected. It is therefore important that psychosocial counseling services are made available to them so that they are able to cope with the situation and continue to take good care of children affected by nodding syndrome under their custody.

In order to streamline the management of nodding syndrome cases, health cadres who come in contact with these children should be trained on basic stipulated care guidelines which should include: assessment of the nature and frequency of head nodding or seizures, feeding habits, presence or absence of infections, assess for malnutrition (anthropometry and record), provide counseling to parents or caretakers and advice them on next steps such as regular growth monitoring and community support visits. Where possible a community or family visit should be conducted to monitor activities of the sick child in the context of the home/natural environment.

The hygiene and sanitation of home environment and the community in which children live, more especially children affected by nodding syndrome should be evaluated and improved if necessary. This includes provision of clean and safe water, safe disposal of human wastes, safe preparation and handling of food and hand washing after visiting the latrine and before handling food. These practices will help prevent the occurrence of diarrheal diseases therefore safeguarding the health and life of children with nodding syndrome.

Head nodding in children with nodding syndrome is reportedly triggered by presence of food or cold temperature. It is therefore important to ensure that

children affected by nodding syndrome have adequate clothing and bedding to keep them safe from drastic weather conditions like low temperatures that could elicit head nodding.

Encourage and facilitate household food production through provision of seeds, increased farming and rearing of small livestock. In the event that families do not have farm implements support should be sought from relevant authorities and bodies to make these available. This will enhance diet diversification at the household level leading to reduced occurrence of nutrient deficiency in all children but more importantly vulnerable groups like children affected by nodding syndrome.

Due to mental retardation and cognitive impairment reported in children affected by nodding syndrome access to learning facilities (education) services may be limited if not absolutely absent. In order to provide learning opportunities to children affected by nodding syndrome a conducive and friendly environment that supports children with disability should be established, skilled teachers recruited, day care and re-education facilities provided and child stimulation services made available to the children affected. This however should be discussed between the community and the ministry of education.

4.4 FURTHER RESEARCH

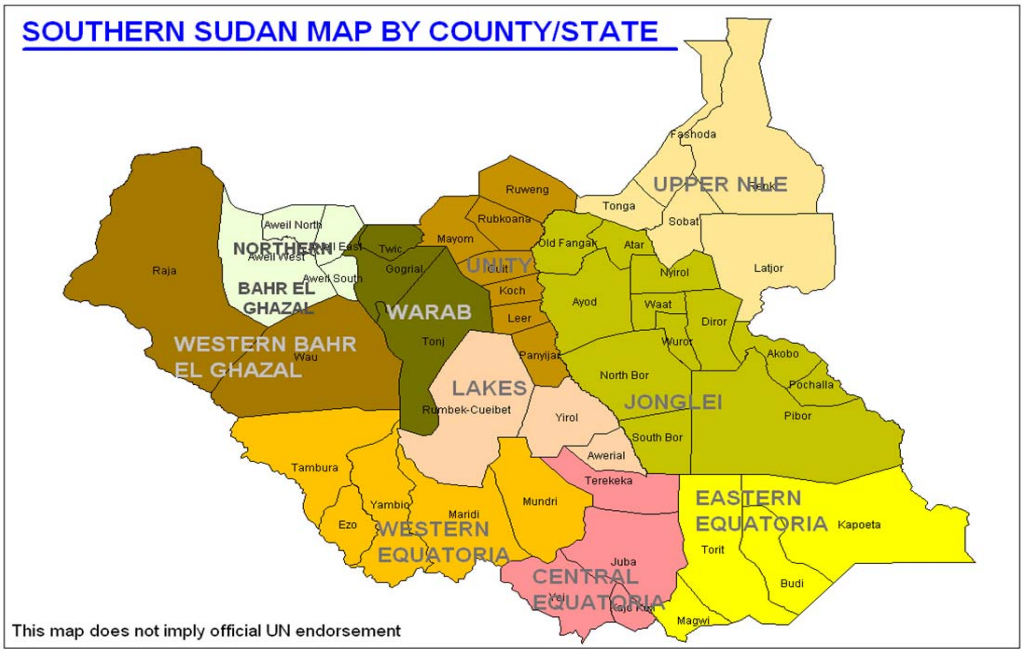
- Further longitudinal research should be conducted to understand the relationship between nodding syndrome and malnutrition; is there temporality?
- Further investigate the relationship between nodding syndrome, growth and sexual development. Investigate if hormonal deficiencies contribute to the growth retardation observed in nodding syndrome cases. An assay of growth hormone, thyroid hormone, androgens, estrogens and glucocorticoids should be carried out.
- Study to establish the causative agent or factor associated with nodding syndrome.
- Conduct further analysis of the benefits and safety (guidelines and implications) of using of anti-convulsion drugs in children with nodding syndrome in South Sudan. CDC and the Uganda government have a plan to study the effects of anticonvulsants in children affected by nodding syndrome.
- Conduct an evaluation of the prevalence and incidence of nodding syndrome in affected and surrounding communities. This is vital for planning of services, understand the etiology, the epidemic dynamics, and later on the mortality (causes, rate).

4.5 CONCLUSION

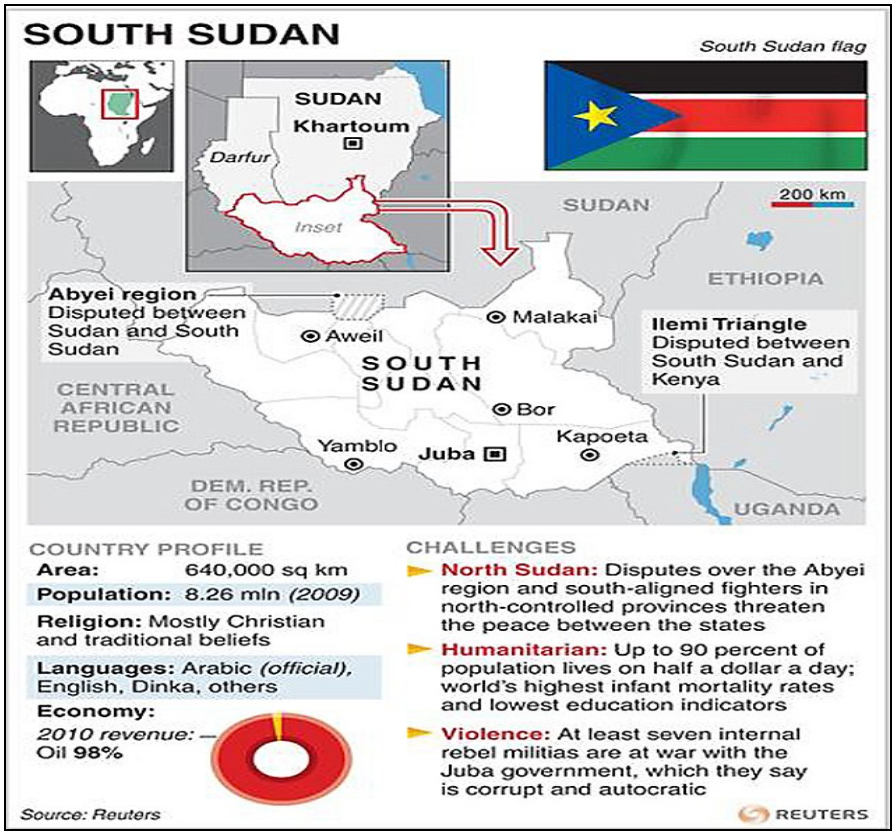
Children affected by nodding are likely to experience growth retardation. In this study it has been noted that the rates of stunting in children with nodding syndrome is very high, above the general population's stunting prevalence, which requires urgent specific remedial actions to halt and reverse the trends. It couldn't however be established if nodding syndrome caused stunting but it was elucidated that rates of stunting (height-for-age z-scores <-2) increased as the duration of illness increased, this in part was due to the design of the study which only established a snapshot of the growth status of children affected by nodding syndrome.

Undernutrition and stunting specifically have severe and life-threatening effects in young children and therefore prevention of these factors should be prioritized in the planning and implementation of children's health and welfare programs. In this case the government, partners and communities should make concerted and unrelenting efforts to follow-up on the welfare of children affected by nodding syndrome, educate parents and communities, train health cadres in the management of children affected, provide necessary medical supplies like anti-convulsion drugs and food supplements, make accessible basic needs like clean water, food and shelter, provide access to a learning environment that is friendly to children affected and where possible conduct further research to establish the etiology of the condition.

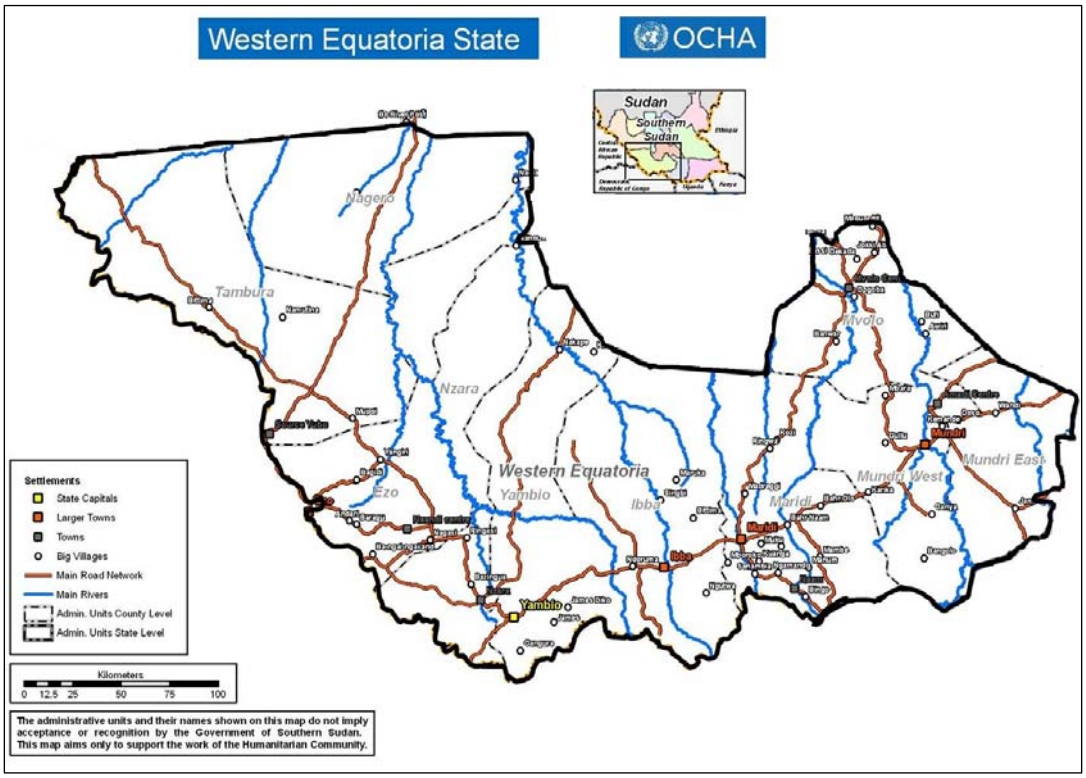
Appendix A:



Appendix B:



Appendix C:


Western Equatoria State
OCHA
Sudan
Southern Sudan
Magenyo
Tambura
Nzara
Ezo
Western Equatoria
Yambio
Ibba
Maridi
Mvolo
Mundri
Mundri East
Mundri West
Settlements
State Capitals
Larger Towns
Towns
Big Villages
Main Road Network
Main Rivers
Admin. Units County Level
Admin. Units State Level
Kilometers
0 12.5 25 50 75 100
The administrative units and their names shown on this map do not imply acceptance or recognition by the Government of Southern Sudan. This map aims only to support the work of the Humanitarian Community.

Appendix D:

Consent form for the Nodding Syndrome investigation in South Sudan

(Flesch-Kincaid Grade Level 6.6)

TITLE: Investigation of suspected nodding syndrome among children in, South Sudan.

SPONSOR: Ministry of Health, Government of southern Sudan (GoSS) and Center for Disease Control and Prevention (CDC), United States

INVESTIGATORS: J. Sejvar, S. Bunga, C. Navarro-Colorado, J. Foltz

Dear Parent / Guardian / Care giver

Your child is invited to be in an assessment which this form will tell you about. This is being done by the Ministry of Health, Government of southern Sudan (GoSS) and Centers for Disease Control and Prevention (CDC), United States. After reading this form, you will have a chance to talk in private with a member of the team. You can ask questions and then decide if you want your child to take part or not.

What are some general things you should know about interviews?

- Study interviews are designed to help doctors learn how to take care of patients better in the future.
- Your child may or may not benefit directly from taking part.
- You are free to agree or disagree from allowing your child to take part or not. If your child participates, you can decide to stop at any time. If you choose not to take part, this will not affect the care that you or your child receives now or subsequently.
- Details about this assessment are below. Please ask the team to explain anything that is not clear.

Why is this investigation being done? This is being done to better understand the clinical and neurological status of children with nodding syndrome and the possible factors (nutrition, birth, and other exposures) that may be related to occurrence of nodding syndrome. Identify the extent of nodding syndrome in the community and how to improve management and care of those affected.

What causes head nodding among children? Nodding syndrome is identified as a type of seizure disorder. Children with NS have nodding of head or different types of seizures. It is known to be possibly associated with river blindness and vitamin B6 deficiency but this has not been confirmed and that is why we are undertaking more investigations.

Who can take part? Any child with head nodding living in Mundri and Maridi regions, S. Sudan, can enroll if they are between 5 and 18 years of age.

How many children will participate? Over a period of about 2 weeks, about 70 children will participate of which 35 will be having nodding syndrome and 35 not having nodding syndrome.

How long will your part last? You will be in the study for <half day from the time you sign up and enroll.

Will I be asked to make any extra visits to the clinic or hospital? Taking part will not involve any extra visits to the clinic or hospital.

What does this interview involve? If you agree to sign up, the following will take place:

- You will sign and date this consent form, agreeing for your child to be enrolled into the study. You and your child will have to spend about half day at the clinic or site of investigation.

While at the clinic, staff will:

- Check for any conditions that could prevent you from taking part.
- Take a detailed clinical history of the child‘s condition (including asking you questions about child‘s head nodding and the progress over past years.
- Do a thorough clinical and neurological examination including height and weight measurements.
- Collect blood, urine, saliva and skin snip samples for various tests.

Test results: You will be given the results of all the tests that your child receives. Someone will talk to you about what the test results mean. They will also help you get further care for your child if needed.

What are the possible risks and discomforts? The collection of blood samples might cause discomfort at the time of sample collection, but it will not hurt. The child may cry after sample collection and very rarely they may bleed from the site for a few seconds but it will stop within less than a minute.

What are the possible benefits of taking part? This work will help doctors learn more about head nodding or seizures among children with nodding syndrome and this understanding may help in identifying the cause of nodding syndrome and enable help in future to identify prevention and treatment measures.

What are the alternatives to taking part? You are free to choose not to take part. If you decide not to take part, you will continue to get the best care currently available from your usual doctor. Apart from what is involved (described above), all of the care you receive will be exactly the same whether or not you decide to take part.

Request for release of medical records: By signing this consent form, you agree to let the team review your child‘s medical records. We will collect information related, which will include your reports on your blood tests and other tests.

How will your privacy be protected? Your name, your child‘s name, and the facts we collect will be kept private to the extent allowed by law. The name will not be written on any sample. After staff fills out a form that contains your medical information, your name will be removed from that form. The samples and forms will be marked with a number that can only be linked to your name by a few people working directly on this work.

Will it cost you anything to take part? Will you be paid to take part? It will not cost you anything to take part in the interviews. For the travel and return (single visit), you will be given $20 as compensation for your time and effort. The staff will give you the $20 when you finish at the clinic.

What if you want to stop before your part is complete? You are free to stop at any time. This will not affect the care that you or your child receives.

What if you have questions about the investigation process? You have the right to ask questions and get answers at anytime during the investigation or thereafter. If more questions come up after talking to staff today, you should call the County Health Director at your locality.

Caregivers Assent (for subject child)

The above has been explained to me. I agree for my child to take part. I had a chance to ask questions. They are all answered. I am told that I am free to decide if I

want to take part. I have also been told that I can drop out at any stage. If I start and do not want to go on, I can do so. This will have no effects for my child. It is explained to me that any information collected will be kept confidential (private) to the extent allowed.

I agree to have:

- A detailed current and past medical history and information on environment, demographics of my child taken.
- My child‘s blood and skin snip taken for tests and other investigations done on my child,
- Staff look at my child‘s medical record and copy down information

If you agree circle YES while if you do not agree circle NO. YES/NO

Full name of caregiver: _____

Relationship to the child: _____

Subject‘s signature or thumb mark: _____

Date: _____/_____/ 20_____ Time: _____h_____

(For those who are unable to sign their name, a witness must verify and sign below.)

I have read and explained the consent form to the person named above and watched them make their mark.

Name of interpreter/ witness: _____ Date: _____/_____/ 20 _____

Signature of interpreter/witness: _____ Date: _____/_____/ 20 _____

Name of investigator: _____ Date: _____/_____/ 20 _____

Signature of investigator: _____ Date: _____/_____/ 20 _____

Appendix E:

Nodding Syndrome – southern Sudan

Case-control questionnaire

CHECKLIST

□ Section 1 – Define case or control status

□ Section 2 – Consent

□ Section 3 – Socio-demographics

□ Section 4 – Family Tree (separate station)

□ Section 5 – Anthropometry and Photo (separate station)

□ Section 6 – Exposures

□ Section 7 – Cognitive evaluation

□ Section 8 – Laboratory investigations (separate station)

Thank you for coming in today. We appreciate the effort you took to get here today and the time it takes to participate in this investigation. By talking with you and your child, we hope to learn more about the syndrome people have been calling Nodding Syndrome. Your child may not have nodding syndrome but you may know someone who does have the disease. We hope that this will help us understand what is causing Nodding Syndrome, how to treat those who have nodding syndrome, and how to prevent other children from developing this unfortunate disease. May I ask you some questions?

1 Yes □

2 No □

Section 1 – Define case or control status

Name of person completing form: _____
Date _____

Nodding Syndrome CASE Definition:

□ A child <18 years with:

□ Head nodding is defined as repetitive *dropping* of head (ask caretaker to demonstrate and 2 team members witnessed)

□ Definitive neurological abnormalities in addition to head nodding such as loss of developmental milestones, other witnessed seizures, objective neurological exam findings such as spasticity, ataxia, or other clear neurological signs.

□ Developmentally normal before the onset of NS

□ Has had NS for not more than 3 years

CASE 1.1. Is this form being completed for a case? Y / N

Nodding Syndrome CONTROL Definitions (1 control per case):

□ Village (Boma) control

□ Within 2 years of the case age

□ No evidence of head nodding, seizure or any other objective neurological abnormality.

□ Who lives in the same village (Boma) as the case

□ From a household with no cases of nodding syndrome.

CONTROL 1.1. Is this form for friend control Y / N

S. No: _____ Assign Case or Control ID. _____

Section 2 – Consent

Section 3 – Socio-demographic variables:

3.1 ID.....

3.2 Date of Birth (DD/MM/YYYY): __ __ /__ __ / __ __ __ __

3.3 Age..... 3.4 Sex..... 3.5 Birth order.....

3.6 Village/Boma..... 3.7 Payam.....

3.8. County .....

3.9 Name of House Hold Head.....

3.10 Education level of:

Mother ..... Father ..... Primary income-earner .....

3.11 Occupation of:

Mother ..... Father ..... Primary income-earner .....

3.12 Annual household income (local currency).....

(or a modification that will measure the income indirectly – To CONSULT local in-country experts)

3.13 Religion: 1 Catholic □ 2 Protestant □ 3 Muslim □ 4 Animist □ 5 Other □ _____

3.14 Ethnicity (check one):

□ Moru □ Morokodo □ Biti □ Avokaya

□ Wadi □ Makaraka □ Sopi □ Lari

□ Modo □ Beli □ Baka □ Zande

□ Adio □ Mondo □ Dinka □ Others _____

3.15 What is the Mother's ethnicity? _____

3.16 What is the Father's ethnicity? _____

Section 4 – Family Tree

4.1 Please draw a family tree of the child, (including the parents' other children). Go up to 3 generations. Include ages and any diseases (especially nodding, epilepsy/fits/seizures and also mental/cognitive impairment by asking if any of the family members are unable to attend the school and if yes, List them all and for each ask and record why?).

* Nodding syndrome

** Siezures / fits, but *no Nodding*

→ This patient

_____ Related (having the same parents or grand-parents or great grand-parents)

X Deceased

□ Male

o Female

4.2 Are mother and father related? Yes □ No □

If yes, Describe how? _____

4.3 Are any of the grand-mother and grand-father pairs related? Yes □ No □

If yes, Describe how? _____

Section 5 – Anthropometry & Photo

5.1 Height: _____ cm 5.2 Mid-Upper Arm Circumference: _____ cm

5.3 Weight: _____ kg

Section 6 – Exposures

Name of person completing form: _____
Date: _____

Think back to when the nodding symptoms first began in the case:

6.1 When did the head nodding first start in the case (if this is a control, then copy the date from the case's answer)? Year_____ Month_____

6.2 Where was this child living at the time the head nodding started (or was noticed first)?

Village/Boma: _____ Payam: _____
County: _____

(If this is a control, tell the respondent the month and year symptoms began in the matched case)

At that time was the child in a camp? □Yes □ No Name and location of the camp _____

6.3 Did your child eat <u>*unripe*</u> sorghum **before** _____ / _____ ***(say month and year when nodding syndrome started in case)***?

□Yes □ No If YES, how frequently (mention per week) _____

6.4 Did your child eat <u>*crushed roots*</u> **before** _____ / _____ ***(say month and year when nodding syndrome started in case)***?

□Yes □ No If YES, What are they? (Name the root/s) _____

How frequently? (Mention per week) _____

6.5 Has your child ever taken INH or Isoniazid?

Yes □ No □ Don't Know □

6.6 Has your child ever taken treatment for tuberculosis (TB)?

Yes □ No □ Don't Know □

If yes, when

_____

6.7 Was there any time from birth to age 2 years old that this child went hungry because he/she did not have food to eat? Yes □ No □

If yes, # of times it happened _____ and give details (when & duration)_____

___

6.8 In the month preceding _____ / _____ ***(say month and year when nodding syndrome started in case),*** what was the main source of food for your household? *(tick all that apply)*

Own farm □ Bought □ Food aid only □ "Other" category □

_____

6.9 List all the places the child has lived (for >3 months) since birth. (Mention village or IDP or Refugee camp, county, State, Country)

S.#	Address of the place Was it an IDP or Refugee camp	Age at the time	Duration

6.10 Was the mother of the child ever at any IDP camp (or in a conflict/war zone) during the duration of pregnancy with this child? □ If yes then, # of times _____ and list below:

# of times_____

Period of pregnancy_____

Duration of Stay_____

Name and location of camp_____

6.11 Was your child exposed to munitions of any type **before** _____ / _____ ***(say month and year when nodding syndrome started in case)***?

YES / NO

If yes, was your child exposed to

Gun-raids? YES / NO

Munitions chemical dump? YES / NO

Bombs, rockets, fuels, propellants or other bomb making material?

YES / NO

Some other type of munitions or chemicals? YES / NO

Please describe this exposure:

_____

How old was the child when this exposure occurred?_____

Where was the child living when this exposure occurred? _____

(Collect information if it was camp or usual residence and get name & address of location)

_____

6.12 During the ante-natal period of pregnancy with this child, did the mother

Consume unripe sorghum □Yes □No □ Don't know Describe_____

Consume Crushed roots □Yes □No □ Don't know Describe _____

Get exposed to munitions □Yes □No □ Don't know Describe _____

Take Ivermectin treatment □Yes □No □ Don't know Describe _____

Take any other medication □Yes □No □ Don't know Describe _____

If yes to any of the above, give details:

_____

6.13 Was there a time when the child's mother went hungry because she did not have food to eat during pregnancy with this child? Yes □ No □

If yes, # of times it happened _____ and give details (when & duration)_____

6.14 Place of Birth:

Village/Boma: _____ Payam: _____

County:_____

6.15 Has the child ever been hospitalized for any serious illness?

□Yes □No □ Don't know

If yes, what was the illness? _____ At what age did it occur? _____

6.16 Has the child suffered from febrile convulsions or other fits before the age of 2 years? Y / N

6.17 When was your last meal? Mention no. of hours back from the time of interview _____ hrs

What did you have in that meal (list all the food items)

_____

6.18 Did you receive any supplements or multivitamins (for example plumpy-nut, sprinkles) in the last 24 hours? □Yes □No □ don't know

If yes, what? _____

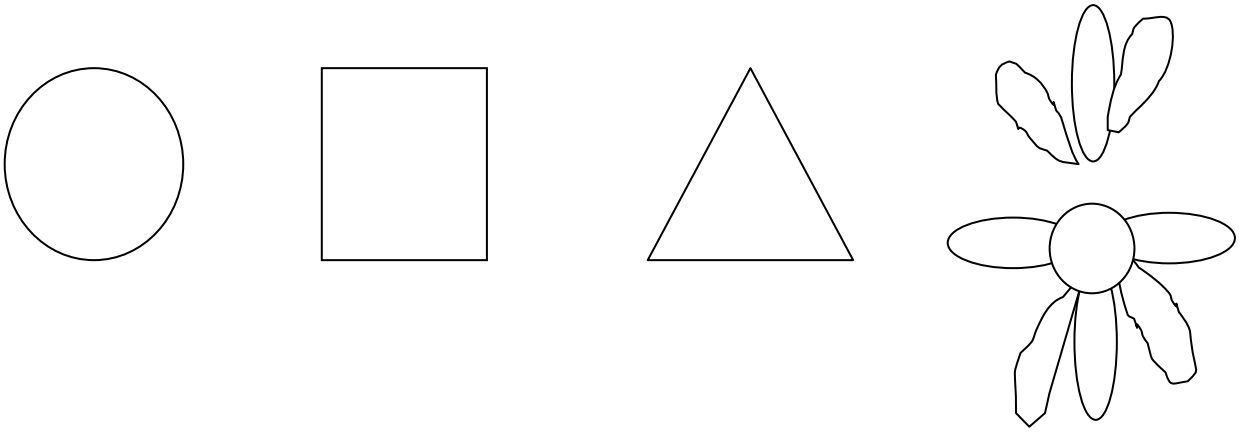
6.19 Did your child eat small fish **before** _____ / _____ ***(say month and year when nodding syndrome started in case)***? □Yes □ No If YES, how frequently (mention per week) _____

Mention the type of the fish _____

Section 7 – COGNITIVE EVALUATION

Name of evaluator: _____

Copy the following drawings:



Ask the child to name as many *different* animals as they can in 60 seconds

Number of animals named: _____

Tell the child the following sequences of numbers *once* and ask them to repeat it back to you:

4	☐ Correct	☐ Incorrect
8 – 1	☐ Correct	☐ Incorrect
1 – 6 – 7	☐ Correct	☐ Incorrect
2 – 5 – 8 – 3	☐ Correct	☐ Incorrect
4 – 2 – 9 – 1 – 6	☐ Correct	☐ Incorrect

Ask the child to tap their index finger and thumb together as fast as possible for 15 seconds (one person should keep time while the other count taps).

Number of taps: _____

Ask the child to identify 3 different colors (red, yellow, blue)

Number correct: _____

Q. DO YOU KNOW ANYONE WHO GOT CURED OF NODDING SYNDROME?

□**Yes** □ **No**

Section 8 – Laboratory investigations

8.1 Blood 8.2 Skin snip 8.3 Urine

8.4 CSF 8.5 Saliva

Appendix F:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

1/27/12

As Principal Investigator of the assessment of Nodding Syndrome investigations, I authorize Godwin Mindra to use the data collected by Center For Disease Control and Prevention (CDC) during the Nodding Syndrome investigations in the field between May and June 2011 in collaboration with South Sudan Ministry of Health.

Godwin Mindra will analyze and report the referred data only for the purposes of writing a Masters of Public Health thesis at the Rollins School of Public Health, Emory University, as part of his International Emergency Refugee Health Branch (IERHB) Complex Humanitarian Emergencies Fellowship. Godwin Mindra will work in direct coordination with, and under the supervision of, the CDC team that implemented the investigation, with Scott Dowell as Principal Investigator and Carlos Navarro-Colorado as fellowship mentor, in addition to standard MPH and thesis supervisory arrangements already made at Emory University.

Scott Dowell
Director
Principal Investigator

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