PEER REVIEW HISTORY

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Nodding Syndrome in Kitgum District, Uganda: Association with Conflict and Internal Displacement
AUTHORS	Spencer, Pete; Landis, Jesa; Palmer, Valerie

VERSION 1 - REVIEW

REVIEWER	Andrea S Winkler Department of Neurology Technical University of Munich Germany
REVIEW RETURNED	21-Aug-2014

GENERAL COMMENTS	Strengths and Limitation: "Diagnostic accuracy of Nodding Syndrome probably very high because of distinctive clinical signs." This needs to be questioned. Please refer to the report of a community-based study on NS in Uganda published in MMWR July 2014, that showed significantly less cases than expected. In addition, many of the cases were not witnessed by health professionals and by the inexperienced eye can easily be mixed up with complex partial seizures or psychiatric disorders. Also, the authors refer to cases before the diagnostic guidelines on nodding syndrome were agreed during the Kampala Meeting in 2012. Introduction: Lines 6-10: The statement on the epilepsy epidemics would need revision as this is not a frequent phenomenon and often is not based on scientific grounds. The quoted reference is not appropriate. Lines 36-39:Please use the prevalence rates from the community-based study recently published in MMWR July 2014 as these are likely to be more accurate. This showed a prevalence of 6.8/1000 children compared to 13/1000 as quoted in the present study. Methods: Lines 5-11: The data in terms of nodding syndrome cases as obtained from the Ugandan Ministry of Health are most likely exaggerated. Although the authors cannot change their data

	acquisition procedure, this needs to be acknowledged. Also, how were new cases of NS determined? Reported by health workers? Where to? Was there mandatory reporting? Results: Lines 36-37: This statement does not seem to be correct and should read…NS appeared 5 and 8 years respectively after… Table 1 and Figure 1: The numbers of case fatalities are difficult to believe. Does it mean that the number of fatalities was only 160/year in the most severe year? Please define what you mean by fatality. Number of people that died? Table 1: What about numbers of NS cases until 2014; there are available from the MoH Conclusion: Lines 7-13: Can the authors explain the "association" of NS and gardening? How could this predispose to a neurotoxic syndrome? Acknowledgment: It is stated that P.S.S. has written the manuscript. How come that this is not the first author?

REVIEWER	Gustavo C. Roman Houston Methodist Hospital, USA
REVIEW RETURNED	04-Sep-2014

GENERAL COMMENTS	Based on published reports from a number of sources, the authors describe a possible relationship between the annual incidence of Nodding Syndrome (NS) in Uganda and the annual number of conflict incidents and fatalities in preceding years. Of note, a decline in incidence has reportedly occurred after the peace agreement in 2008. The authors believe that the clinical diagnosis is obvious but an epidemiological definition has been agreed upon only recently (CDC). Moreover, the prevalence mentioned by the authors (12/1000) seems too high. The CDC study obtained a prevalence of 6.8 and 7.2/1,000 for suspected and probable NS cases respectively in three districts in Uganda (Iyengar et al. Prevalence of nodding syndrome--Uganda, 2012-2013. CDC's MMWR 2014 Jul 18;63(28):603-6.). Based on their research the authors postulate a strong association between NS and use of garden food, but no reason is given for garden food to induce NS. There is no mention of recent studies that have suggested onchocerciasis (Korevaar DA, Visser BJ. Reviewing the evidence on nodding syndrome, a mysterious

	tropical disorder. Int J Infect Dis 2013;17:e149-52). The authors also conclude that NS is temporally associated with war, in agreement with recent reports that include a possible neuropsychiatric cause induced by the emotional traumas of war, poverty and frustration over neglect (Van Bemmel et al. Ethn Health 2014;19:100-18; Musisi et al. Neuropsychiatric perspectives on nodding syndrome in northern Uganda: a case series study and a review of the literature. Afr Health Sci 2013;13:205-18). In summary, the conclusions of this paper are far from clear: if the authors believe that NS is toxic-nutritional and linked to consumption of garden food this should be clearly mentioned. The temporal association with wartime is obvious and the possibility that NS results from the neuropsychiatric impact of childhood PTSD should be mentioned. Finally, by mentioning cannibalism are the authors raising an analogy with kuru and a possible prion infection? Was cannibalism explored? Page 6 line 37, should read "causal" not casual References should be updated.

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

COMMENT 1.1: Strengths and Limitation: "Diagnostic accuracy of Nodding Syndrome probably very high because of distinctive clinical signs." This needs to be questioned. Please refer to the report of a community-based study on NS in Uganda published in MMWR July 2014, that showed significantly less cases than expected. In addition, many of the cases were not witnessed by health professionals and by the inexperienced eye can easily be mixed up with complex partial seizures or psychiatric disorders. Also, the authors refer to cases before the diagnostic guidelines on nodding syndrome were agreed during the Kampala Meeting in 2012.

RESPONSE 1.1. Reference to the contents of the 2014 MMWR is now included.

COMMENT 1.2: Introduction: Lines 6-10: The statement on the epilepsy epidemics would need revision as this is not a frequent phenomenon and often is not based on scientific grounds. The quoted reference is not appropriate.

RESPONSE 1.2: Reference to "epidemics" has been removed.

COMMENT 1.3: Lines 36-39:Please use the prevalence rates from the community-based study recently published in MMWR July 2014 as these are likely to be more accurate. This showed a prevalence of 6.8/1000 children compared to 13/1000 as quoted in the present study.

RESPONSE 1.3: The findings of the 2014 MMWR are now included, and the apparent earlier MOU overestimation of NS prevalence is now stated.

COMMENT 1.4: Methods: Lines 5-11: The data in terms of nodding syndrome cases as obtained from the Ugandan Ministry of Health are most likely exaggerated. Although the authors cannot change their data acquisition procedure, this needs to be acknowledged. Also, how were new cases of NS determined? Reported by health workers? Where to? Was there mandatory reporting?

RESPONSE 1.4: The exact method by which the MOU defined a case of Nodding Syndrome is not known to the present authors; this is now stated.

COMMENT 1.5: Results: Lines 36-37: This statement does not seem to be correct and should read…NS appeared 5 and 8 years respectively after…

RESPONSE 1.5: The numbers of years have been adjusted to mesh with the data provided.

COMMENT 1.6: Table 1 and Figure 1: The numbers of case fatalities are difficult to believe. Does it mean that the number of fatalities was only 160/year in the most severe year? Please define what you mean by fatality. Number of people that died?

RESPONSE 1.6: The conservative method by which the number of fatalities (people who died in conflicts) is recorded by ACLED was stated as a study limitation in the Discussion. A statement regarding this limitation now appears in both the Methods and Discussion.

COMMENT 1.7: Table 1: What about numbers of NS cases until 2014; there are available from the MoH.

RESPONSE 1.7: While numbers of NS cases from 2011 to 2014 are of considerable interest, they are outside the scope of this study (1997-2011). Additionally, case numbers from 2011 to 2014 are not available to the present authors. Interpretation of NS case numbers from 2011 to 2014 would be difficult because the MOH appear to have changed their criteria for case definition, from a MOH case definition (1998-2011), to an international consensus definition (from August 2012), to a MOH-CDC-modified international consensus definition in 2013.

COMMENT 1.8: Conclusion: Lines 7-13: Can the authors explain the “association” of NS and gardening? How could this predispose to a neurotoxic syndrome?

RESPONSE 1.8: While Spencer et al. (2103) recognized and extensively discussed the possible role of environmental, nutritional, and infectious factors in Nodding Syndrome, the present Discussion mistakenly focused only on nutritional factors. There was and is no intent to identify a neurotoxic

etiology for Nodding Syndrome. The Discussion has been adjusted to recognize the possible role of factors other than nutrition and food quality, notably infection with Onchocerca volvulus.

COMMENT 1.9: Acknowledgment: It is stated that P.S.S. has written the manuscript. How come that this is not the first author?

RESPONSE 1.9: The first author, a junior investigator, identified the key data used in this paper. It is a common scientific practice for the senior author to draft the manuscript, followed by discussion, review and editing by other authors.

REVIEWER #2

COMMENT 2.1: The authors believe that the clinical diagnosis is obvious but an epidemiological definition has been agreed upon only recently (CDC). Moreover, the prevalence mentioned by the authors (12/1000) seems too high. The CDC study obtained a prevalence of 6.8 and 7.2/1,000 for suspected and probable NS cases respectively in three districts in Uganda (Iyengar et al. Prevalence of nodding syndrome--Uganda, 2012-2013. CDC's MMWR 2014 Jul 18;63(28):603-6.).

RESPONSE 2.1: Reference to the contents of the 2014 MMWR is now included.

COMMENT 2.2: Based on their research the authors postulate a strong association between NS and use of garden food, but no reason is given for garden food to induce NS. There is no mention of recent studies that have suggested onchocerciasis (Korevaar DA, Visser BJ. Reviewing the evidence on nodding syndrome, a mysterious tropical disorder. Int J Infect Dis 2013;17:e149-52). The authors also conclude that NS is temporally associated with war, in agreement with recent reports that include a possible neuropsychiatric cause induced by the emotional traumas of war, poverty and frustration over neglect (Van Bemmel et al. Ethn Health 2014;19:100-18; Musisi et al. Neuropsychiatric perspectives on nodding syndrome in northern Uganda: a case series study and a review of the literature. Afr Health Sci 2013;13:205-18).

RESPONSE 2.2: While Spencer et al. (2103) recognize and extensively discussed the possible role of environmental, nutritional, and infectious factors in Nodding Syndrome (including onchocerciasis, an observation reported in 2002 by the WHO team – which included Spencer -- investigating Nodding Syndrome in then-southern Sudan), the present Discussion mistakenly focused exclusively only on nutritional factors. There was and is no intent to propose a neurotoxic etiology for Nodding Syndrome. The Discussion has been adjusted to recognize the possible role of factors other than nutrition and food quality, notably infection with Onchocerca volvulus. The CDC investigators provided no explanation of the significance of the association they reported between Nodding Syndrome and use of food from gardens (versus food purchased or provided by the World Food Programme). The Van Bemmel et al. paper is now included.

COMMENT 2.3: In summary, the conclusions of this paper are far from clear: if the authors believe

that NS is toxic-nutritional and linked to consumption of garden food this should be clearly mentioned. The temporal association with wartime is obvious and the possibility that NS results from the neuropsychiatric impact of childhood PTSD should be mentioned. Finally, by mentioning cannibalism are the authors raising an analogy with kuru and a possible prion infection? Was cannibalism explored?

RESPONSE 2.3: The major conclusions, namely an association with war and internal displacement, are clearly stated and support the original objectives of the present study. The delayed temporal association between peaks of conflict, fatalities, internal displacement and Nodding Syndrome has not been reported before. The association of Nodding Syndrome with onchocerciasis (originally reported in then-southern Sudanese cases by a WHO team that included the senior author of the present study, see Tumwine et al., 2012 and Spencer et al., 2013) was mistakenly omitted from the Discussion and is now included. The authors did not intend to imply that Nodding Syndrome is a toxic-nutritional disorder; indeed, the etiology is unknown and investigation should include infectious, nutritional, toxic, and neuropsychological factors (the Musisi et al., 2013 report referenced in the Introduction is retained), as the revised manuscript now states. The authors are not implying a prion infection (a subject discussed by Spencer et al., 2013) either from consumption of primate or human tissue. To the extent cannibalism occurred in Acholi Sub-Region, it is noteworthy that no reports have surfaced that connect this practice with Nodding Syndrome.

COMMENT 2.4: Page 6 line 37, should read “causal” not casual.

RESPONSE 2.4: This typographical error is corrected in the revised manuscript.

COMMENTS 2.5: References should be updated.

RESPONSE 2.5: Two recently published papers have been included, together with a reference to the 2012 Kampala international consensus report on the diagnosis of Nodding Syndrome to which the senior author contributed.

References cited in Responses to Reviewers’ Comments

Spencer PS, et al. Afr Health Sci. 2013 Jun;13(2):183-204.
Musisi S, et al. Afr Health Sci. 2013 Jun;13(2):205-18.
Tumwine et al. Afr Health Sci. 2012 Sep;12(3):242-8.