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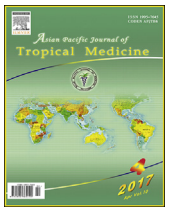

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Needs of exploring the burden of recent onset seizures due to neurocysticercosis and challenges in southeast Asia focusing on scenario in Malaysia

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ABSTRACT

Seizures due to neurocysticercosis (NCC) is a neglected human-to-human transmitted disorder and an emerging problem worldwide. A substantial portion of recent onset seizures is known to be attributed to NCC in *Taenia solium* (*T. solium*) endemic areas where populations which neither raise pigs nor eat pig meat are also at risk. High prevalence of NCC causing epilepsy has been reported in the underdeveloped areas of Southeast Asia (SEA) however, only fragmentary information on its incidence is available in countries like Malaysia. In Malaysia *T. solium* infection was previously thought to be infrequent due to Muslim population majority and the religious prohibition of consuming pork, but it is not totally absent. There is an evident lack of knowledge and awareness of the actual burden, routes of transmission, and the impact of NCC in this region. The problem is assumed to be more prevalent particularly in cities because of the frequent inflow of possibly *T. solium* infected individuals or carriers among those who migrate from neighboring endemic countries to Malaysia. The issue of imported cases that are likely to be emerging in Malaysia is highlighted here. An accurate quantification of regional burdens of epilepsy due to NCC in Malaysia is warranted considering the disease emergence in its neighboring countries. It is suggested that the importance of NCC be recognized through quantification of its burden, and also to collect epidemiological data for its subsequent elimination in line of World Health Organization's mission for control of cysticercosis as a neglected tropical disease. In this review the need as well as a strategy for neuro-care center screening of epilepsy cases, and various issues with possible explanations are discussed. It is also proposed that NCC be declared as a reportable disease which is one of the eradicable public health problems in SEA.

1. Introduction

Today it is a well-documented fact that neurocysticercosis (NCC), the *Taenia solium* (*T. solium*) metacestode larval infection in central nervous system (CNS) is an important cause of acute epilepsy in humans, particularly in the tropics [1–4]. Currently, there is no sufficient evidence available in order to project NCC's global prevalence. However, a recent meta-analysis which summarized the proportion of NCC among persons with epilepsy (PWE) suggested that in endemic communities nearly one-third of PWE are living with *T. solium* cystic lesions in their brain [5].

Though the magnitude of NCC burden in endemic countries is high, its neurological involvement is being recognized only recently as an important but neglected cause of epilepsy [6]. As per WHO estimation of 50 000 deaths due to *T. solium*, neural involvement was assumed to be the major reason [7], making NCC the single most important cause of acute epilepsy in developing countries. It is prevalent in Latin America, a major part of Asia (including China and the Southeast Asia), Eastern Europe, and most of Africa [2–4] with seroprevalence rates

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reaching up to 25% in general populations in areas known to be endemic for *T. solium* [8].

In addition, NCC is also emerging in geographical areas which were never known to be endemic for this parasite [9,10]. Controlled studies using CT scans in Ecuador, Honduras, and Peru have demonstrated strong association between NCC and seizures, with up to 30% of seizures attributable to NCC [2–4]. This rate was similar to studies from other endemic countries which have estimated prevalence of NCC among PWE to be between 25 and 50% [11,12]. There were also reports revealing NCC prevalence in apparently healthy communities in previously unexplored provinces as in the case of Port-au-Prince in Haiti; 2.8% of general population were identified to be clinical cases of NCC [13]. These reports are making governments in many other never explored countries realize the potential endemicity of this infectious disease.

In developed countries, NCC is diagnosed more frequently among immigrant populations [14,15]. As reported in western countries, it occurs in small outbreaks [16]. NCC has been found in 10% of new-onset seizure patients in California [17,18]. More than 1000 new cases are being detected in the United States every year [19]. Surprisingly, its prevalence is also on the rise in Muslim countries; especially in the Gulf region because of the heavy reliance on laborers from highly endemic neighboring countries [20–22]. Hence, NCC is no more limited to tropical regions, religion and/or economic status of the affected communities. This situation reinforces the urgent need for a global initiative of screening programs and regulations which warrant compulsory reporting of new cases.

In the SEA region, the potentiality of human to human transmission of *T. solium* infections is of concern in this review. Among the known *T. solium* endemic regions in Asia, particularly Bali in Indonesia is reported to be of high importance due to the risk of transmission of infection to tourists [23]. However, the likelihood that Malaysia might also be sub-endemic for this disease which is not yet explored. Indigenous cases of *T. solium* taeniasis/cysticercosis were initially thought to be infrequent in Malaysia. However, this problem might be more prevalent in future since there is an increase in tourism and population movements. The proportion of infection might be less compared to neighboring endemic countries in Asia or other endemic tropical countries; however that likelihood of underestimating its prevalence in this country should be addressed. In this review, the need for screening PWE in order to estimate the cysticercal burden of recent onset seizures in SEA and challenges of the present time are discussed. Also a strategy is suggested for neurocare center screening from among epilepsy cases for an etiological confirmation and a compulsory reporting of NCC in this region.

2. The need to screen recent onset seizures patients for cysticercal etiology in SEA

NCC is known to be one of the major preventable causes of adult onset epilepsy in tropical developing countries that is presently a public health threat crossing international boundaries. SEA is an endemic region for NCC with widespread economically underdeveloped areas. It has been reported that pork consumption in SEA has considerably increased over the last decades [24]. There are many small-holder farming communities with inadequate hygiene practice, poor pig management, and lack of meat inspection as well as control. Given that there is evident lack of knowledge and awareness of the actual burden, routes of transmission, and the impact of NCC in SEA, there is an urgent need to screen epileptic patients for NCC in order to fill this gap of information.

The burden of *T. solium* taeniasis/cysticercosis either in general communities or in epileptic patients has been documented in Indonesia [25–30], Thailand and Myanmar [31–41], Lao People's Democratic Republic (Lao PDR) [42–45], Cambodia [46–51], Vietnam [52–58], Taiwan [59], and Philippines [60–62]. Thus many of countries in SEA are known to be endemic for taeniasis/cysticercosis. However only recently some proposals being raised to pay attention on the prevention and control of this NTD [63,64]. Other than the SEA region, *T. solium* taeniasis and particularly NCC as a major contributor of recent onset seizures in other major countries in Asia are widely documented in India [65–76], China [77–84], Nepal [85–99]. A recent review on cysticercosis/taeniasis endemicity in SEA describes a country-wise prevalence picture [60].

In SEA, as in other parts of the globe, there is continuous migration towards cities or international destinations according to season, crop harvest time, or other routine activities. SEA is a target for travel and immigration from neighboring countries for various reasons that include but not limited to trading, technological collaboration development, education, and employment. For example, there is a large immigrant population working in Malaysia – legally and illegally. Some of the immigrants may be tapeworm carriers and they work in Malaysian cities as cooks and food handlers or vegetable/fruit sellers. Most of the time, immigrants from neighboring countries obtain employment without undergoing thorough/any health screening or treatment. This is the main reason for the possible dissemination of infection into urban communities. Some of these workers might be domestic helpers in the urban cities of Malaysia. They may not be aware of the underlying infection and they can spread the disease to the local population. This problem is not confined to the inflow of migrants to Malaysia as outbound travel of local population to other countries is also increasing again for the various reasons. A large segment of the Malaysian populations consists of descendants of immigrants and they maintain close contacts with their places of ancestry. Often they travel to places in neighboring SEA countries endemic for NCC where they might be acquiring this parasitic infection.

In Malaysia, recent case reports indicated an emergence of NCC as diagnosed in major medical centers [100–104]. The most recent one was a pediatric case of seizure which underwent surgery for excision of the live worm [101]. These studies indicated a possible inflow of immigrants being one of the reasons for the NCC caused recent onset of acute epilepsy (AE) in Malaysia. An epidemiological study in a rural province of Sabah, Malaysia Borneo indicated evidence of exposure to the parasite in the local population (cysticercosis antibodies = 2.2%) [105]. In a recent screening study by our group, a positive anti-cysticercus antibody in serum has been detected in 3.5% (20 of 572) of indigenous communities in peninsular Malaysia [64]. A personal communication with Neurocare Division of University of Malaya Medical Center in Kuala Lumpur (Malaysia) revealed 3 cases of confirmed NCC in recent time, of which 2 were detected among Malaysians, and one case was in an Indian nationality (unpublished observation by Devaraj Pancharatnam). Besides that, few clinically and radiologically suspected cases attending neuromedicine clinics were also available in hospital record

even though those were not surgically proven as cysticercosis, and thus never reported even if tested positive serologically. Incidence of ophthalmic cysticercosis is also reported in Malaysia [102]. Therefore, cysticercosis in Malaysia is believed to occur in either native or immigrants populations. But the true prevalence scenario with confirmatory diagnosis of the etiology is never explored. Moreover, serological positive rate might be highly variable from study to study because of the lack of quality diagnostic antigens or inconsistency in diagnostic reagents used by different researchers as suggested elsewhere [106]. Because these few cases were only diagnosed in hospitals from restricted part of this country, however, this iceberg tip is tempting to explore the way up to its base provided a larger screening program is set with a scope to screen high risk communities.

Given that epilepsy is a major problem in SEA including Malaysia and that PWE have high unemployment rates, and many are in part-time or low-income employment [107], it will be beneficial to determine the possible cysticercal burden of epilepsy in this region so that appropriate treatment management can be initiated.

The current burden and distribution of NCC, its public health importance as well as the economic relevance need to be properly documented in SEA including Malaysia in order to highlight its importance, and to bring it to the attention of affected communities, decision-makers and funding agencies. Therefore if information regarding the burden of epilepsy due to NCC is generated, then probably the burden can be reduced if there is any attempt taken to eliminate the underlying infectious agent. Hence a regional surveillance program for cysticercosis is of a great need for Malaysia and other unexplored regions in SEA. Screening acute epileptic patients for possible NCC followed by analysis of the patient demographics might be helpful in tracing its source of transmission to provinces where no much information is available so far.

3. Challenges

Since there is an increasing acknowledgement of the neurological burden imposed by cysticercosis recently, it has demanded large-scale control and elimination programmes worldwide [108]. In this mission, a better estimate of taeniasis/cysticercosis NCC burden as obtained by brain imaging can be ensured by inclusion of individuals with NCC infection who are asymptomatic carriers. Newer diagnostic materials and/or tools might be employed for a more accurate diagnosis. Thereby, preventive measures of epilepsy in CNS infections can be explored [66]. Various issues that might hinder screening and reporting of NCC among epileptic patients, and possible explanations are discussed below.

3.1. Sociocultural and religious issues

There is an assumption that NCC in humans does not occur in countries in which religious laws prohibit pig breeding and consumption of pork, so the disease has been considered nonexistent in Muslim countries. Malaysia is known to be a predominantly Muslim country and a similar assumption might be prevailing in this country. However, the above assumption might be a challenge when non-muslim residents and/or expatriates are concerned because, NCC is a disease most often acquired via ingested of eggs excreted by humans infected with the adult tapeworm in his/her intestine, meaning it can be transmitted without pork consumption (an infected pig can only perpetuate the infection causing intestinal taeniasis) [2]. Hence it is not surprising that vegetarians can also acquire cysticercosis [109]. Recently, emerging cases of NCC in previously nonendemic Muslim countries are autochthonous [110]. As in the case of Arabian Peninsula where many recent cases were reported in wealthy Muslim families who employed babysitters and housekeepers from disease endemic areas, it is likely that some were adult *Taenia* carriers who transmitted the infection through unhygienic practices of food handling or directly by the fecal oral route [110]. Although pig husbandry is regulated in Malaysia, it is hypothesized that *T. solium* carriers from neighboring endemic areas who enter this country every year might infect native communities and increase the prevalence on NCC with or without infected pig involvement. Hence, in Malaysia, the actual prevalence and incidence of NCC is unknown, and it may be worth considering that many of the cases might not have been reported.

3.2. Issues with prioritization and clinical management

Similar to NCC, epilepsy is also under-recognized, however it is an increasing burden on the welfare and economies in the developing world [111]. Thus prioritization of epilepsy remains a challenge for public health policy and practice in many developing countries. Cost-effectiveness of the control strategy for cysticercosis-related epilepsy is therefore very high [55]. For both NCC and epilepsy, there is a dilemma always whether limited resources should be better utilized on general economic development that is expected to have a broad impact on the health and welfare of people, or on specific programs to help affected individuals with NCC and epilepsy. Either approach requires a thorough economic evaluation [111]. It may not be optimal to demonstrate a causal association between epilepsy and infections in CNS. Rather underlying structural basis, pathogenesis, and prognosis of epilepsy must also be defined. Moreover, it is also necessary to consider the effectiveness of antimicrobial agents for treating infections, and anti-convulsive drugs on seizure outcome [112]. There is a lack of “full time” epileptologists as well as paucity of neurologists and neuroradiologists with interest in presurgical evaluation in Malaysia and probably in many parts of the SEA. Also there is a skewed distribution of neurology manpower in Malaysia as documented elsewhere [113]. So a lack of adequate resources and interest might affect the establishment of etiological information of epilepsy in this region.

3.3. Issues with public awareness, attitudes and knowledge toward epilepsy

Practice of treating PWE in the developing world may be different from that in developed countries. The knowledge and attitudes of PWE are well known to impact outcome of any management practice associated with seizure control [114]. In a past study on surveying public awareness, knowledge and attitudes (AKA) toward epilepsy in a rural state of Malaysia (predominantly Malay population), the respondents were found to be familiar with epilepsy, however majority of them

demonstrated a negative attitude and also they had poor knowledge on the causation and available treatment options of epilepsy [115]. In order to gauge the current insight regarding epilepsy among rural communities in Malaysia, again a study reported the outcomes of those signifying the necessity to devise a dedicated education program on epilepsy for implementation among rural communities [116]. Authors proposed an increased AKA level in society to improve people's acceptance rate, minimize stigmatisation, and improve health-related quality of life (HRQoL) for epileptic patients as well as their families. Findings from another survey also showed that AKA might play a challenging role that influences patients' HRQoL, suggesting that epilepsy treatment management plans should also focus on improving AKA by means of awareness campaigns in order to improve the overall health outcomes [117]. A global action plan for treatment, stigma reduction and improvement of HRQoL should be set-up in this country.

3.4. Issues with diagnostic confirmation of NCC

NCC can be a potential cause of refractory seizure which at times may be difficult to diagnose even if it is not common in many countries. In Malaysia, it poses a diagnostic challenge as it is claimed that this disease is not seen amongst the local population; however with the arrival of immigrant workers, a number of cases have been diagnosed [99]. That is why, the clinical presentation of seizure and brain imaging should be taken as priority over blood investigations for diagnosing NCC, and advanced neurosurgical intervention might be useful [100]. With a continuously increasing migrating population from other countries, now it has become even more important to have a heightened awareness of this particular disease, especially in patients presenting with recent onset of epileptic seizures [103]. Hence, in non-endemic areas, clinicians those caring for refugee or immigrant populations should suspect NCC in PWE in general, or among those with chronic headache, and/or other unexplained neurologic manifestations [41].

The majority of cases with NCC do not show typical imaging features and also solitary brain lesion is often a diagnostic challenge [118]. Hence it is very important to choose an appropriate imaging modality for a correct diagnosis of the etiology in PWE [119]. In resource-poor locations, MRI might not be performed for all types of brain lesion taken into consideration of its availability as well as cost factors. Also co-existence of two common ring-enhancing lesions in the same patient with typical imaging features may be possible [120]. TWO major diagnostic challenges are: (1) routine hospital based detection and treatment monitoring; and (2) diagnosis and monitoring in screening and control studies in endemic communities. Conventional diagnosis of NCC needs a relevant clinical history, positive serological test result, and brain imaging [121].

Commonly, estimation of the prevalence of any infectious disease is hampered by variable degrees of sensitivity and specificity of each of the tests used, which might find a limited or overlapping proportion of the true prevalence. Indeed, several helminthic species can cause CNS infections and all of these might cause seizures [122]. Molecular techniques have not yet been proven useful to diagnose NCC particularly in clinical settings. Alternatively immunological tests should be able to discriminate infections with live forms of the parasites from those with inactive or degenerated forms, and should also be correlating with parasite load, for clinical management and post-treatment follow-up [123]. Therefore, understanding the extent of the burden of NCC among patients with recent onset seizures and identifying the communities that would benefit from possible control measures need a specific diagnosis. Biological stage or the stage of degeneration is also a challenge for serological diagnosis [124]. Immunosenescence could be another challenge [125]. There may be a group of individuals which are seropositive with no evidence of neurological symptoms or supportive findings upon imaging. Seropositivity with no evidence of neurological disease might indicate a sub-clinical infection, a state of protective immunity, or cysticercosis outside of the CNS [126]. It is also possible that most of the infected hosts produce multiple antibodies of different specificities that might be appearing at different time points following infection; apparently antibodies of varying specificities are developed in response to the qualitative and quantitative changes in various antigen types released during different developmental stages of the parasite in the brain [127]. Moreover diagnosis of an early stage infection is a challenge.

3.5. Issues with mass anti-helminthic treatment

WHO has recommended mass treatment with praziquantel (PZQ) for control of *T. solium* taeniasis and cysticercosis. However there might be safety issues. In past there are records of individuals dying within days following treatment as part of mass treatment campaigns against schistosomiasis and/or fish-borne trematodiasis in SEA countries [128]. But there have been no information on analyzing the cause of sudden deaths in those treated individuals. If those drug trial areas were also endemic for taeniasis/cysticercosis, then sudden deaths could have been due to underlying NCC by which the individuals succumb due to a side effect of PZQ treatment since, in those cases, PZQ could have resulted in acute seizures or convulsions when given without a steroid [29]. Therefore it is necessary to reconsider the possible adverse effects of PZQ for treatment of NCC. Particularly during campaigns for parasite control with mass anti-helminthic treatment it is essential to consider possibility of numerous individuals in the community having NCC but with no symptoms [106,128].

4. Recommendations

As of now only few number of cases of NCC reported among patients with seizures in Malaysia. Besides that reported cases of ophthalmic and other forms of cysticercosis are also few, Moreover the serological evidence of cysticercosis are reported in some remote communities only. So one may argue on paying attention on this problem in a countrywide scale based on few cases only. But now the debate is on whether we should consider NCC as one of the differential in screening epileptic patients in this region for an etiological confirmation or not. Also the debate is on the relevancy of initiating a countrywide epidemiological program in Malaysia in order to assess the actual burden of NCC causing seizures in this region. It can be suggested that a prospective database of patients with NCC in a group of hospitals in Malaysia if shows that it is a significant cause of epilepsy alone will probably justify any program to look into this disease in greater depth. Similar initiatives might be necessary in other

parts of the SEA where no previous information available on prevalence of NCC causing seizures.

However, the real problem is that lack of awareness, under recognition of the parasitic cause of epilepsy, and poor reporting contribute to the wrong estimate of its actual burden. When we consider NCC as a global problem in the current time, then probably we must remember this as one of the differential among patients with recent onset seizures particularly when there is a suspicion based on the travel history and/or passible exposure to the parasite eggs irrespective of whether we know or do not know about its prevalence in the country of residence of any patient. As discussed previously, it is being reported in an increasing number in previously known non-endemic countries. Moreover in the current review we intend to justify initiation of studies in different parts of Malaysia since this is also one of the countries that is unexplored in the SEA region and is at risk of cross boundary transmission from neighboring countries known to be endemic for *T. solium* infections.

In the proposed WHO mission for control of NTDs, one important task of the present time is collection of better data on its burden across the globe [129,130]; particularly in countries of suspected endemicity or those where emergence of cases are reported. With respect to the SEA and Western Pacific Regions, recently, WHO has placed importance for taeniasis/cysticercosis control under its Regional Action Plans (2012–2016) of the NTDs control and elimination (correspondence). Hence, a strategy for a compulsory notification will have major advantage of providing an accurate estimate of its prevalence at the regional level in a suspected endemic areas, thereby permitting a rational use of resources in the global campaigns for the eradication [131]. Also we need to develop cost effective but sensitive diagnostic strategies for differentiating either old or new asymptomatic conditions that might be helpful in mass population surveillance studies [124]. There is a need of establishing a better strategy for diagnosis of taeniasis/cysticercosis by highly reliable molecular techniques as recommended by Akira Ito in the context of the disease burden in Asia [128].

Also a vast degree of variation in the neuropathological mechanisms of the disease, and symptoms of NCC often makes it difficult to diagnose and treat in clinical practice [132]. Hence there is a current need to provide an assessment of the burden of NCC among PWE in few pockets in the endemic region particularly which are never explored before or even regions which were previously assumed to be non-endemic for *T. solium* cysticercosis. For example in a recent study in Bhutan, NCC has been reported to be associated with 6%–25% of epilepsy in cohort study [133]. Qatar is a small country on the Eastern coast of the Arabian Peninsula where NCC is thought to be non-native. However there are recent reports recommending NCC to be considered in the etiological differential diagnosis of epilepsy particularly in patients coming from SEA [134]. It is suggested elsewhere that specific epilepsy protocols should be considered to increase the diagnostic yield of neuroimaging in patients with structural lesions associated with focal or generalized seizures [135].

Since epilepsy is documented to be a major problem in SEA and NCC which is one of its preventable causes, it is hypothesized to be re-emerging in this region due to various reasons discussed earlier. Therefore, there is a need of a proper strategy quantifying its actual burden which is possible if initiated from the neurocare centers. The first step in this mission includes screening and identification of cases presenting with seizure followed by confirmation of the etiology and reporting (Figure 1).

Other possible infectious causes of seizures must be considered in differential diagnosis. Cysticercosis must be considered in diagnosis of soft tissue cystic nodules or masses where data regarding sizes of lesions might be helpful in differentiating NCC from other soft tissue lesions and on MRI as suggested elsewhere [37,136]. Implementation of a validated questionnaire for investigation of epilepsy and its etiology is

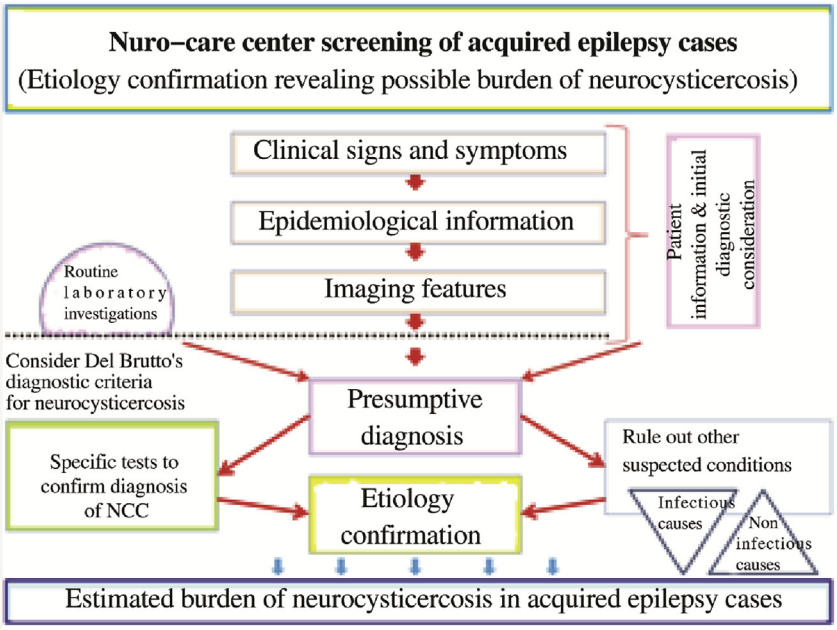

Figure 1. A Strategy for Estimating Burden of Epilepsy Due to Neurocysticercosis.
*Del Brutto's diagnostic criteria includes viz., absolute, major, minor, and epidemiological; interpretation of these criteria permits two degrees of diagnostic certainty: (1) definitive diagnosis (having one absolute criterion/two major plus one minor and one epidemiological criteria); and (2) probable diagnosis (having one major plus two minor criteria/one major plus one minor and one epidemiological criteria/three minor plus one epidemiological criteria) [121].

necessary. Once the communities at high risk are identified, then rapid diagnostic tests can be employed to screen the population at risk in Malaysia/other SEA countries. The public health as well as economic relevance of *T. solium* cysticercosis must be defined prior to action planning for its control. Hospital record based data collection, and information from slaughterhouses are also essential [14]. A national registry in each of the countries will be of a great advantage for proper recording and analysis to establish an actual prevalence. A reinforcement of the universal guidelines suggested for diagnosis of NCC, declaration of NCC as an international reportable disease, and also standardizing data collection methods could improve our understanding of the actual global burden of NCC supporting the recommendations done earlier [5].

5. Conclusion

Though the causal link between CNS infections and seizures is known previously, for cysticercosis, the link has been recognized recently. Now it is time to be alert for this neglected but preventable cause of epilepsy in SEA and to join hands in line with the elimination programme for NTDs as per WHO's vision 2020. Even in provinces where pork consumption is legally prohibited, NCC should be considered in the differential diagnosis for etiologies in all those patients with relevant neurological symptoms, especially in countries sub-endemic for *T. solium* or with a large expatriate population as in case of Malaysia. Hence, it is recommended that NCC should be included among diseases of public health importance in the regional programme of surveillance of communicable diseases. Considering the cross boundary transmission of infections, it is now essential to explore the actual burden of recent onset seizures due to NCC in SEA and it should be declared reportable.

Conflict of interest statement

The authors declare no conflict of interest.

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