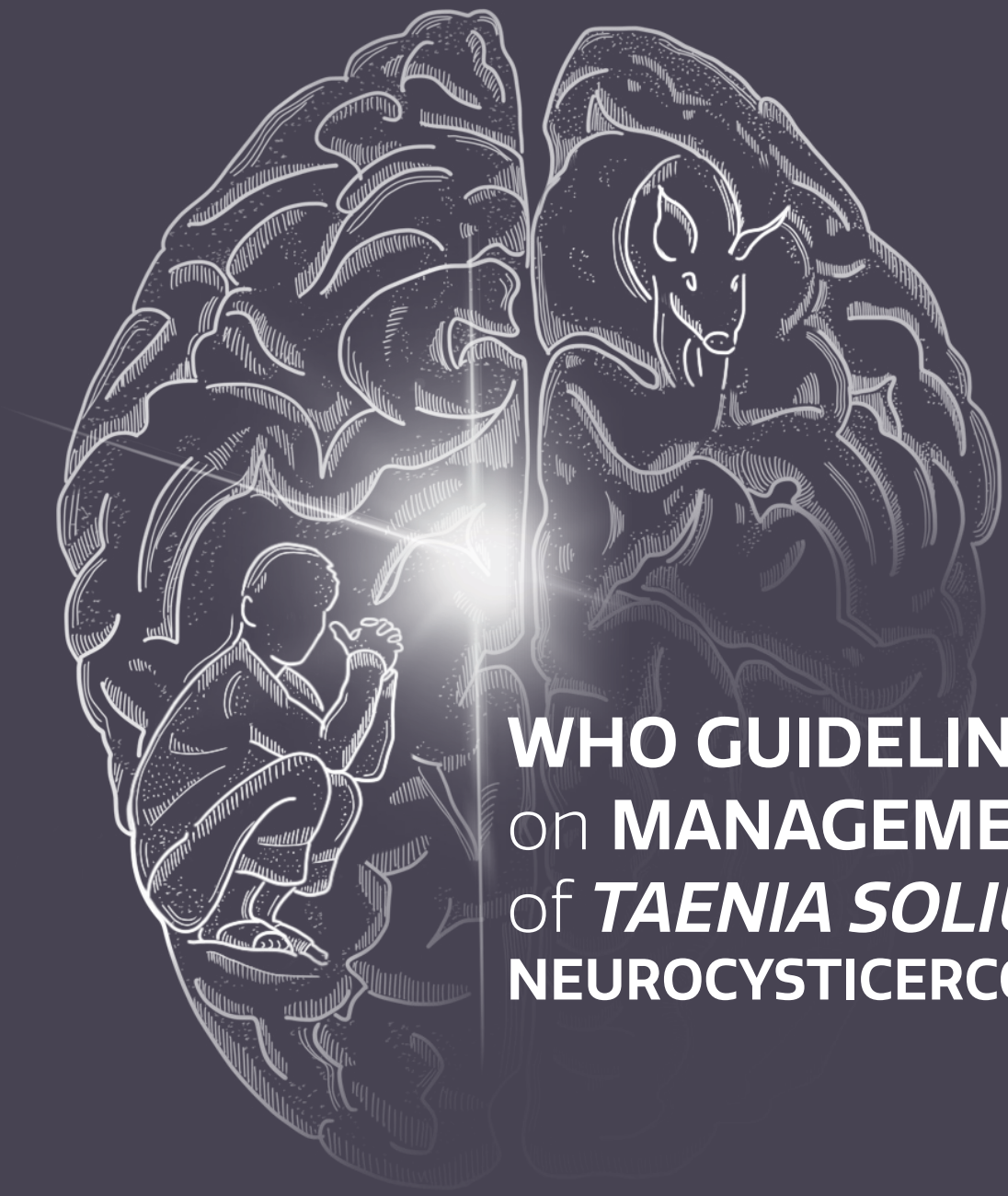
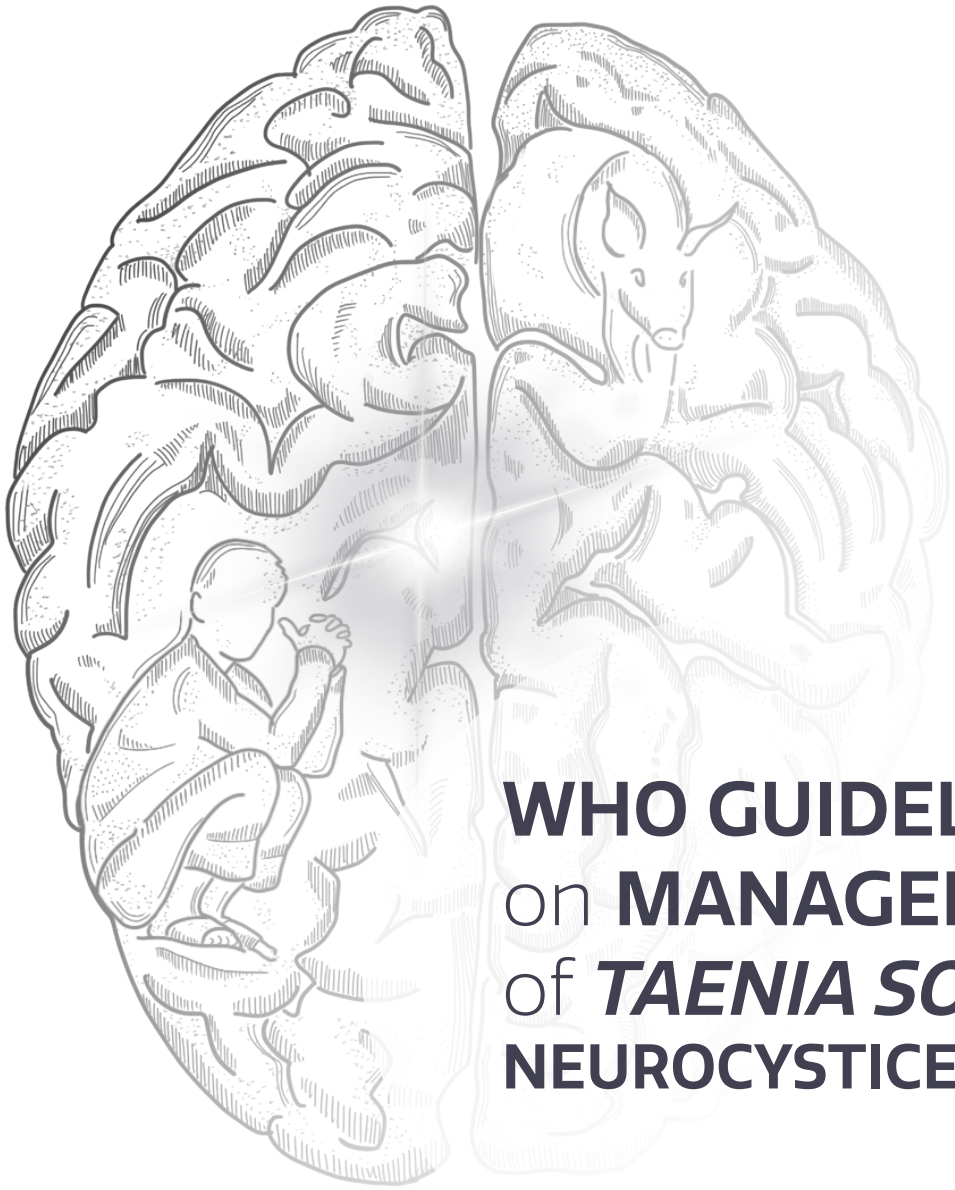


WHO GUIDELINES on MANAGEMENT of *TAENIA SOLIUM* NEUROCYSTICERCOSIS

World Health Organization



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WHO guidelines on management of *Taenia solium* neurocysticercosis

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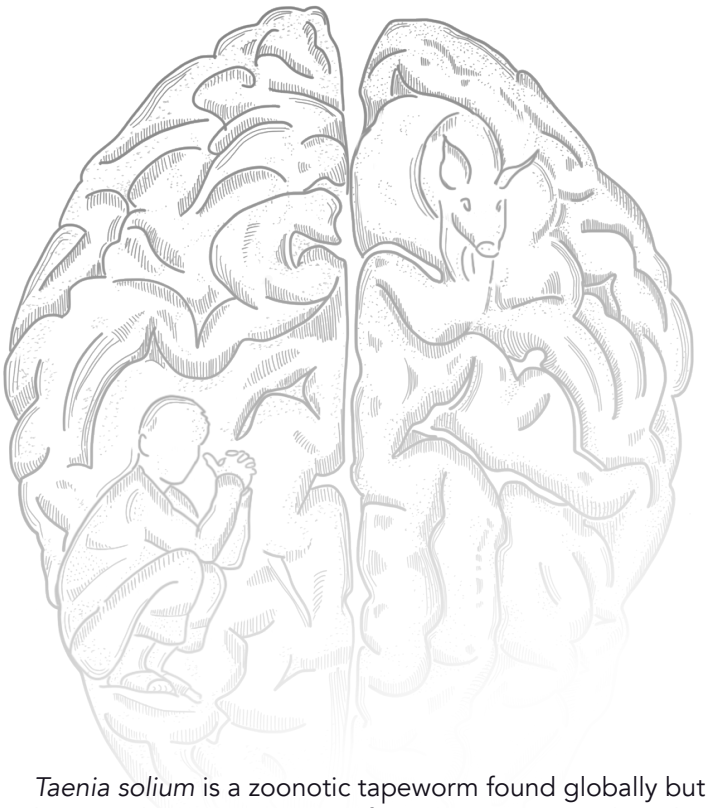
ABBREVIATIONS and ACRONYMS

AED	antiepileptic drug
ALB	albendazole
CI	confidence interval
CT	computerized tomography
DXM	dexamethasone
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LMIC	low- and middle-income countries
mhGAP	Mental Health Gap Action Programme
MRI	magnetic resonance imaging
PICO	population, intervention, comparator, outcome
PRED	prednisolone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PZQ	praziquantel
RCT	randomized controlled trial
RR	relative risk
SEL	single enhancing lesion
WHO	World Health Organization



EXECUTIVE SUMMARY

BACKGROUND

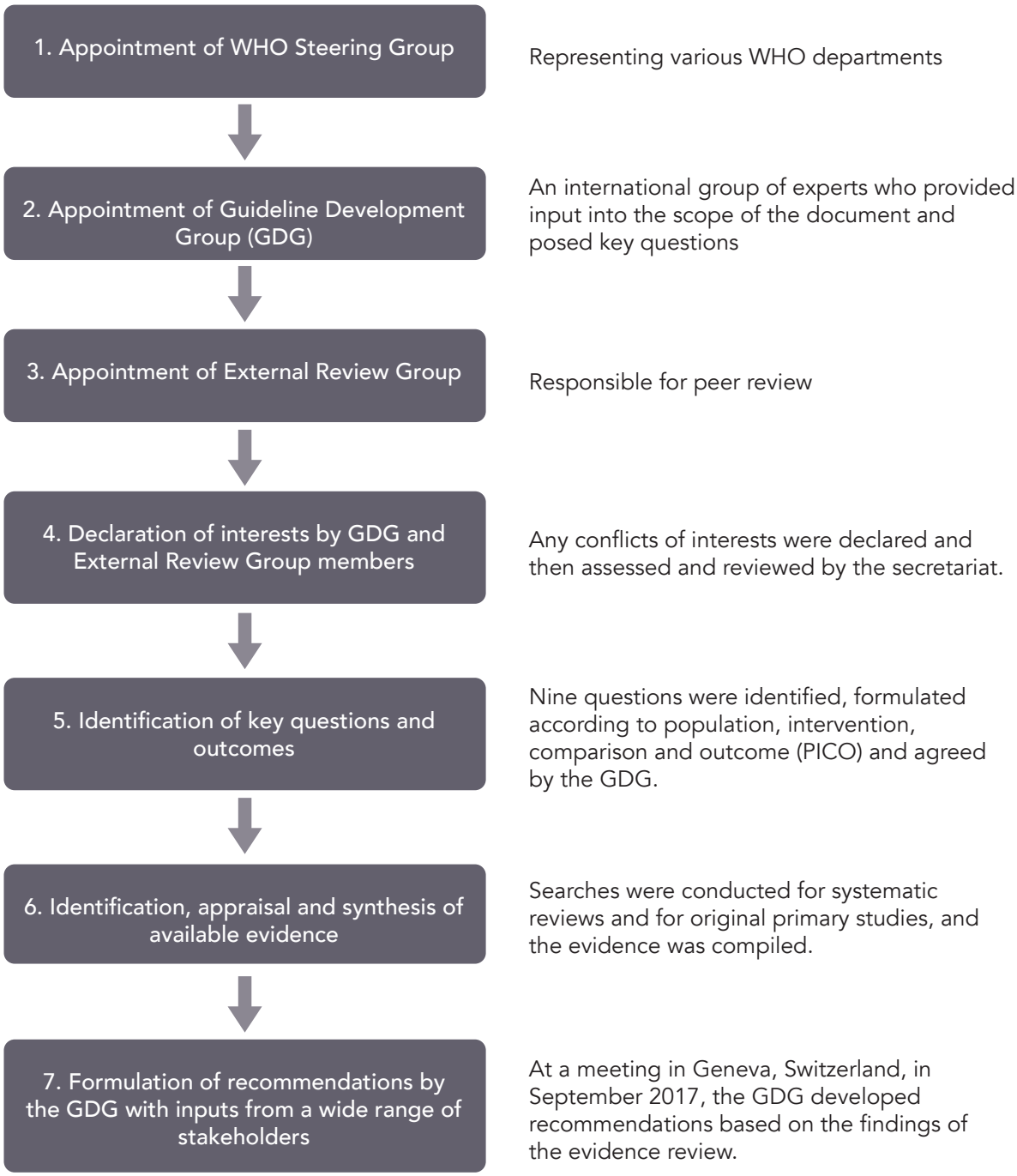
Taenia solium is a zoonotic tapeworm found globally but with particularly high transmission and hyperendemnicity in parts of Latin America, South and South-East Asia and sub-Saharan Africa *(2)*. Depending on its life cycle, it causes two distinct presentations in humans: taeniasis and (neuro) cysticercosis. Although people with taeniasis do not have severe disease, they shed *T. solium* eggs, which can infect both pigs and humans. The resulting larvae form cysts in the muscles, skin, eyes or central nervous system (cysticercosis). "Neurocysticercosis" refers to the development of *T. solium* cysts in the human central nervous system, which causes focal epilepsy, epileptic seizures, hydrocephalus, chronic headaches, focal deficits and symptoms associated with increased intracranial hypertension. Neurocysticercosis is one of the leading preventable causes of epilepsy worldwide, estimated to contribute to up to 30% of epilepsy cases in areas where the disease is endemic *(3, 4)*. The total number of people with symptomatic or asymptomatic neurocysticercosis is estimated to be 2.56–8.30 million, according to the available data on the prevalence of epilepsy *(5–7)*. These numbers may, however, be underestimates because of poor access of the groups at highest risk to diagnostic tests. Given this wide range, better understanding of the disease and its control is crucial, as is recognition of the lack of accurate information and the importance of more data on neurocysticercosis epidemiology.

The internationally recognized criteria for diagnosis of neurocysticercosis include a requirement for neuroimaging techniques, such as computerized tomography (CT) and/or magnetic resonance imaging (MRI), ideally supported by serology. These facilities are not available in all settings, especially in rural areas of low-income countries, making it difficult to identify and treat patients. Additionally, there is controversy about the role, type and duration of anthelmintic, anti-inflammatory and antiepileptic drug (AED) treatments for different forms of neurocysticercosis.

These guidelines were developed to assist health-care providers in appropriate, evidence-based management of parenchymal neurocysticercosis. The guidelines do not address other forms of neurocysticercosis and do not include management of extraparenchymal disease (including cysticerci in the cerebral ventricles or subarachnoid space). The aim of the guidance is to improve decision-making to ensure appropriate patient care and to avoid misdiagnoses and inappropriate treatment of patients with neurocysticercosis. The guidelines were developed in a collaboration between the WHO departments of Control of Neglected Tropical Diseases and Mental Health and Substance Use.

METHODS FOR DEVELOPING THE GUIDELINES

These guidelines were developed according to the standard WHO procedures, in the following steps:



In step 6, the quality of the evidence was assessed according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) with regard to the study design and the risks of bias, inconsistency, indirectness, imprecision and reporting bias. The quality of the evidence was then characterized as high, moderate, low or very low. The final report of the evidence review was presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In step 7, the GDG followed the standard WHO procedure for making recommendations based on the evidence review.

A planning proposal for diagnosis and treatment guidelines for *T. solium* neurocysticercosis was submitted in 2016. A meeting of the Guideline Development Group (GDG) was held at WHO headquarters in Geneva on 25–26 September 2017, where the systematic review team presented the evidence retrieved in the form of evidence profiles and GRADE tables (see Annex 4) and recommendations were formulated. The GDG used the evaluation of effect and further evidence of harm, benefits, values, preferences, resource use and feasibility to score the strength of recommendations. The strength of a recommendation was set as either:

> "strong", indicating that the GDG was confident that the quality of the evidence of effect and certainty about the values, preferences, benefits and feasibility made the recommendation one that should be followed in most circumstances and settings; or
>
> "conditional", indicating less certainty about the quality of the evidence and the values, preferences, benefits and feasibility of this recommendation and therefore circumstances or settings in which it might not apply.

In order for a recommendation to be strong, the GDG had to be confident that the desirable effects of an intervention outweighed any undesirable effects. When the GDG was uncertain about the balance between desirable and undesirable effects, the members issued a conditional recommendation.

At the meeting in 2017, the GDG advised further review of the evidence and updated systematic reviews for some of the PICO questions. Systematic reviews were therefore conducted up to 2019, delaying finalization of the guidelines.

RECOMMENDATIONS

The final recommendations of the GDG were as follows.

No.	Recommendation	Strength	Quality of evidence
Use of CT scan and MRI for neurocysticercosis diagnosis			
PICO 1	MRI is the tool of choice in the diagnosis of neurocysticercosis, particularly when parenchymal viable, parenchymal granuloma or neurocysticercosis of the cerebellum, brain stem, ventricular, subarachnoid and spinal spaces are suspected. CT is the tool of choice for detecting small calcified lesions. CT should be used as an alternative where MRI is unavailable or contraindicated.	Strong	Not applicable

No.	Recommendation	Strength	Quality of evidence
	Treatment of neurocysticercosis with anthelmintic and anti-inflammatory therapy		
PICO 2 and 3	Anthelmintic therapy[a] in combination with corticosteroids, should be given to individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts for better outcomes in terms of cyst resolution and seizure control.	Strong	Moderate
PICO 4 and 5	Anthelmintic therapy with ALB[b], in combination with corticosteroids, should be given to individuals with symptomatic neurocysticercosis and a single enhancing lesion (SEL) for better outcomes in terms of cyst resolution and seizure control.	Conditional	Moderate to very low
	Treatment of neurocysticercosis-related epilepsy with antiepileptic drugs (AEDs)		
PICO 6	Withdrawal of AEDs should be considered 6 months after the last seizure in individuals with a SEL and epilepsy with low risk of seizure recurrence (defined as patients with a resolved granuloma, no residual calcification and who are seizure free). AED therapy should be continued in people with a SEL that persists on neuroimaging and those with a SEL that resolves with residual calcification. Remarks: There is limited evidence on the optimal duration of AED therapy for a SEL; however, it appears to be a few weeks after complete resolution of the SEL.	Conditional Conditional	Low Moderate
PICO 7	AED therapy should be continued for at least 2 years in people with single or multiple calcified neurocysticercosis and epilepsy. These patients should be closely monitored if treatment is withdrawn.	Conditional	Very low
	Treatment of neurocysticercosis in patients with HIV/AIDS		
PICO 8 and 9	Patients with neurocysticercosis who are coinfected with HIV should be treated according to the guidelines for treating patients with neurocysticercosis without HIV/AIDS.	Conditional	Very low

[a] As per the recommendations in the *Guideline for preventive chemotherapy for the control of Taenia solium taeniasis (8)*, the choice of drug (albendazole [ALB] or praziquantel [PZQ]) by each country depends on factors including drug availability, acceptability, affordability and feasibility of implementation.

[b] No studies with PZQ were found.

RESEARCH PRIORITIES

The extensive search for evidence on the diagnosis and treatment of parenchymal neurocysticercosis yielded useful baseline information but also highlighted significant gaps. The GDG identified the following priorities and questions for further research:

- programmatic research to increase access of high-risk populations to neuroimaging facilities for diagnosis of neurological diseases, including neurocysticercosis;
- randomized controlled trials (RCTs) of the optimal choice and duration of administration of AEDs;
- definition of optimal combinations, dosing and duration of anthelmintic and anti-inflammatory medications;
- determination of optimal AED treatment and withdrawal therapy for patients with calcified neurocysticercosis;
- determination of optimal therapy and/or special considerations for patients coinfected with neurocysticercosis and HIV; and
- in areas where access to imaging is limited and costly, exploration of the use of serology as a first step in diagnosis.

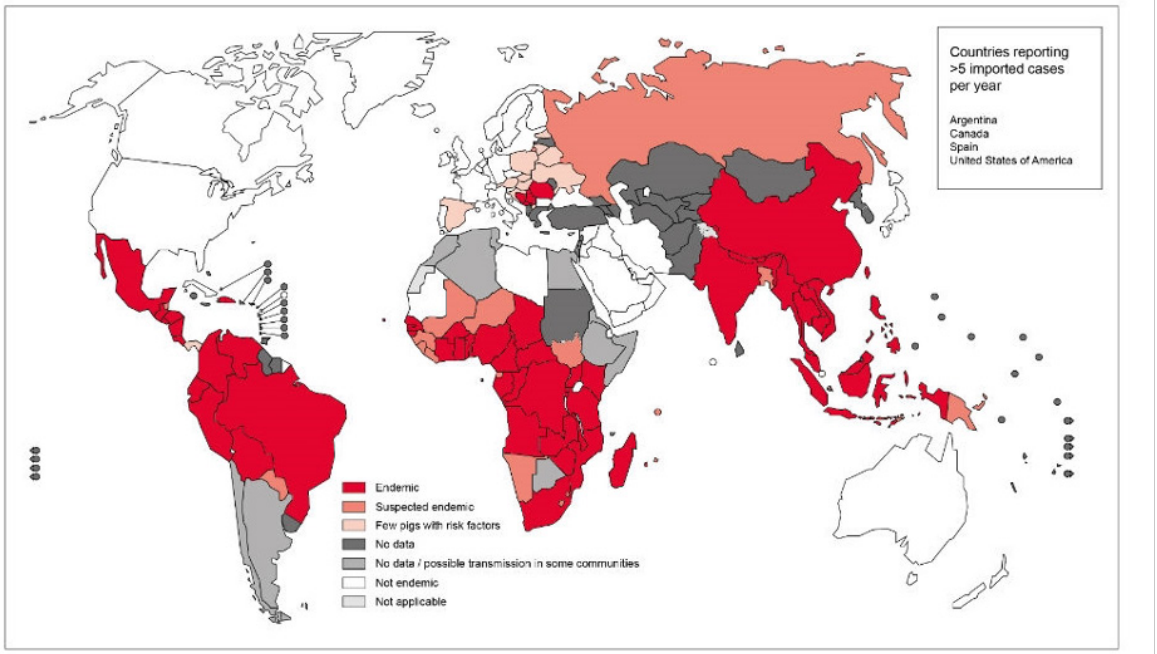


Fig. 1. Endemicity of *Taenia solium*, 2015 (*Source*: reference 9)

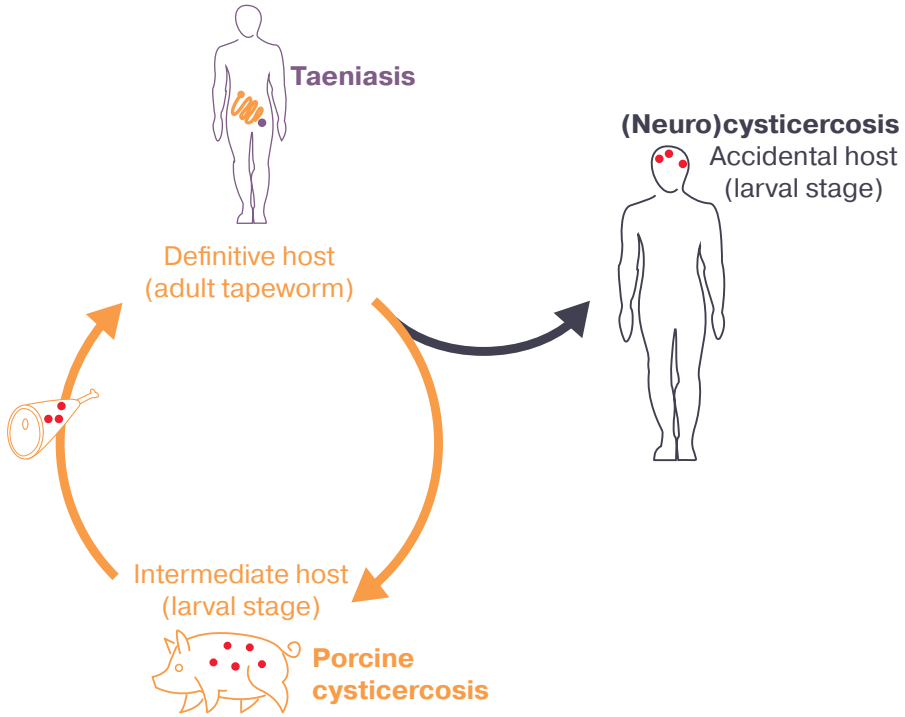


Fig. 2. Transmission cycle of *Taenia solium*

INTRODUCTION

BACKGROUND

Taenia solium is a zoonotic tapeworm which causes taeniasis and cysticercosis in humans. The total number of people with symptomatic or asymptomatic neurocysticercosis is estimated to be 2.56–8.30 million from the data available *(5–7)*. Incongruity among studies, however, demonstrates the extent to which neurocysticercosis remains an understudied, misunderstood, neglected tropical disease *(3)*.

The greatest burden of *T. solium*-induced disease is due to neurocysticercosis, which is estimated to contribute to approximately 30% of epilepsy cases in areas where the disease is endemic. Neurocysticercosis is also an important cause of hydrocephalus in endemic areas.

Diagnosis of neurocysticercosis requires neuroimaging, which is largely unavailable in highly endemic regions. Diagnosis and treatment of neurocysticercosis are also challenged by lack of diagnostic facilities and care (e.g. appropriate point-of-care tests) in endemic areas. Therefore, the prevalence of infection and disease, morbidity and mortality are probably grossly underestimated.

T. solium is a zoonotic tapeworm found globally but with greater transmission and hyperendemnicity in rural areas of Latin America, South and South-East Asia and sub-Saharan Africa *(2)* (Fig. 1). In humans, it has two distinct presentations, depending on its life cycle: taeniasis and cysticercosis. Taeniasis refers to intestinal infection with adult tapeworms and occurs when people eat infected pork that is raw or undercooked. Although taeniasis is not associated with severe disease, people shed *T. solium* eggs, which can infect both pigs and people. The resulting larvae form cysts in the muscles, skin, eyes or central nervous system to cause cysticercosis (Fig. 2); cysts that occur in the central nervous system are termed neurocysticercosis. In humans, neurocysticercosis can result in severe disease, depending on the number, location and burden of cysts and the resulting host inflammatory reaction.

Most neurocysticercosis is asymptomatic *(2)*; however the most common features are seizures. Neurocysticercosis is thought to be the leading cause of preventable epilepsy worldwide and can also cause chronic headaches and hydrocephalus *(10)*. The clinical presentation of neurocysticercosis is pleomorphic. Cysts lodged in different compartments of the brain give rise to unique clinical syndromes that require specific treatment. Parenchymal cysts are most commonly associated with seizures and epilepsy and are more amenable to treatment, particularly if they are viable or degenerating. Extraparenchymal neurocysticercosis is associated with hydrocephalus, meningitis, focal neurological deficits and death if not properly managed. Management of extraparenchymal neurocysticercosis is often more complex than that of parenchymal disease, and treatment often requires neurosurgery as well as medical management.

Epilepsy affects an estimated 23.4 million people worldwide *(11)* and can involve loss of consciousness, acute bowel or bladder dysfunction, injuries or sudden death. It is also associated with social stigmatization and discrimination in many countries. Between 60% and 70% of people with epilepsy respond to treatment *(12)*; however, approximately 80% of people with epilepsy live in low- and middle-income countries (LMICs), and most do not receive appropriate treatment *(13)*. In areas endemic for cysticercosis, neuroimaging reveals lesions of neurocysticercosis in up to 30% of people with epilepsy *(14, 15)*.

Limited data are available on the burden of *T. solium*-induced disease. The estimates of research groups of the number of neurocysticercosis-associated cases of epilepsy globally range from 370 710 (95% uncertainty interval, 282 937–478 123) in 2010 *(4)* to 1.93 million (95% uncertainty interval, 1.60–2.31 million) *(3)* or 8.30 million *(5–7)*. More data, more uniform approaches, more consistent definitions or a combination of these are necessary. The estimates are based on

serological studies; however, detailed population-based studies in endemic areas that have included neuroimaging suggest that estimates based on serology significantly underestimate the burden of disease, especially calcified lesions.

Neurocysticercosis is mainly a disease of poverty that affects predominantly rural populations with poor sanitation. The burden of neurocysticercosis on health systems, economies, societies and individuals due to epilepsy affects the wages and results in health costs and social stigmatization of sufferers and caretakers. The disease also affects pig farmers economically, as they may lose income if they cannot sell infected animals and meat. In 2010, *T. solium* cysticercosis was added to the WHO portfolio of neglected tropical diseases *(16)*. *T. solium* cysticercosis remains a neglected disease because of lack of general awareness, lack of information on disease burden, a paucity of validated tools for field diagnosis and treatment, poor access to neuroimaging and neurological care and hesitation to invest in zoonotic neglected tropical diseases *(17)*.

The control and elimination of *T. solium* are hindered by many factors, including the lack of reliable epidemiological data on infections in people and pigs. No national surveillance or control programme is currently in place, except in China, despite the endemicity of *T. solium* and epilepsy in LMICs (Fig. 1), although many countries have programmes to prevent infected meat from entering markets and public health recommendations to avoid undercooked meat *(18)*. Appropriate surveillance and point-of-care diagnostic tools would enable identification and targeted interventions in high-risk communities. Invasive oncospheres (hatched from infective ova) induce a high level of immunity, and vaccines have been developed from defined oncosphere antigens that confer a high level of protection. These have not been generally developed or included in control schemes because the method of vaccinating swine is inefficient, cumbersome and labour intensive *(19, 20)*.

The greatest burden of *T. solium*-induced disease is due to neurocysticercosis. New cases can be prevented with health and educational community interventions *(20)* and a One Health approach involving:

- vaccination and anthelmintic treatment of pigs to prevent infection with *T. solium* cysticerci;
- improved pig management practices to prevent exposure of pigs to human faeces;
- improved sanitation to prevent contact between pigs or humans and *T. solium* eggs in human faeces and in the environment;
- meat inspection and sufficient cooking of pork to reduce the risk of humans becoming infected;
- treatment of human taeniasis; and
- health education to promote hand hygiene, food safety, sanitation and pig management.

Diagnosis of neurocysticercosis requires neuroimaging techniques such as CT and/or MRI, which are not readily available in many settings where the disease is prevalent. The neurosurgical services required for the most severe cases are even more limited. Evidence now suggests that effective treatment and administration of corticosteroids during and after treatment reduce seizures. The degree of oedema around degenerating cysts predicts a worse outcome, and corticosteroids reduce subsequent seizures and lesion calcification. There is, however, uncertainty about the optimal dose and duration necessary for maximum effect. Information is required on the optimal AEDs to manage patients with neurocysticercosis and the time to withdrawal.

SCOPE AND INTENDED READERSHIP

Aims and objectives

These guidelines provide guidance on the management of parenchymal neurocysticercosis to facilitate implementation of the World Health Assembly resolutions on epilepsy (WHA68.20) and neglected tropical diseases (WHA66.12) by health-care planners and programme managers in affected countries.

The guidelines are for health-care providers working in first- or second-level facilities or at district level, including basic outpatient and inpatient services. Health-care providers include doctors, nurses and other cadres. These guidelines do not address management of extra-parenchymal neurocysticercosis, as this is more severe and requires specialist management in a referral setting.

Policy-makers, health-care planners and programme managers in governments and international agencies could also use these guidelines in implementing the World Health Assembly resolution on epilepsy, the neglected tropical disease road map and the concept of universal health coverage (Box 1). Ultimately, these guidelines for neurocysticercosis management will contribute to strengthening health systems in LMICs. They will also be useful for academics and researchers to inform teaching and research agendas.

Box 1. Available tools and guidelines relevant to the control of *T. solium* cysticercosis

WHO/FAO/OIE guidelines for the surveillance, prevention and control of taeniasis/cysticercosis. Paris: World Organisation for Animal Health; 2005 (https://apps.who.int/iris/bitstream/handle/10665/43291/9290446560_eng.pdf).

Winkler AS, Schaffert M, Schmutzhard E. The pattern of epilepsy in a rural African hospital – an approach adapted to local circumstances. Trop Doctor. 2009;39(1):44–7.

Assembling a framework for intensified control of taeniasis and neurocysticercosis caused by T. solium. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/153237/1/9789241508452_eng.pdf).

Landscape analysis: management of neurocysticercosis with an emphasis on low- and middle-income countries. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/152896/1/WHO_HTM_NTD_NZD_2015.05_eng.pdf).

Update of the Mental Health Gap Action Programme guideline for mental, neurological and substance use disorders. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/204132/1/9789241549417_eng.pdf).

Donadeu M, Fahrion AS, Olliaro PL, Abela-Ridder B. Target product profiles for the diagnosis of *Taenia solium* taeniasis, neurocysticercosis and porcine cysticercosis. PLoS Negl Trop Dis. 2017;11(9):e0005875.

White AC Jr, Coyle CM, Rakshekhar V, Singh G, Hauser WA, Mohanty A et al. 2017 Clinical Practice Guidelines (IDSA, ASTMH) for the diagnosis and treatment of neurocysticercosis. Clin Infect Dis. 2018;66(8):e49–75.

Carpio A, Fleury A, Kelvin EA, Romo ML, Abraham R, Tellez-Zenteno J. New guidelines for the diagnosis and treatment of neurocysticercosis: a difficult proposal for patients in endemic countries. Exp Rev Neurotherapeutics. 2018;18(10):743–7.

Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/338565).

METHODS

MAIN POINTS

- The contributors to the guidelines were multidisciplinary, gender-balanced and representative of all WHO regions.
- Questions were identified to inform recommendations on diagnosis and treatment of neurocysticercosis.
- Systematic reviews were conducted for each of the nine PICO questions.
- The GRADE system was used to assess the quality of the evidence.
- Evidence profiles compiled for each of the nine questions are tabulated in Annex 4.
- Recommendations were made by consensus at the face-to-face meeting in September 2017.

CONTRIBUTORS

Individuals and groups involved in guideline development

The WHO Steering Group comprised staff from the departments of Control of Neglected Tropical Diseases, Mental Health and Substance Use, the Special Programme for Research and Training in Tropical Diseases and the Joint United Nations Programme on HIV/AIDS and from the WHO regional offices. The Steering Group provided administrative support for guideline development, including drafting questions, identifying the systematic review team, overseeing evidence retrieval, assessment and synthesis, selecting members of the GDG, organizing the GDG meeting, drafting the guidelines according to the decisions of the GDG and overseeing peer review, publication and dissemination of the guidelines. Before the guideline proposal was made, members of the International League Against Epilepsy were included in discussions to represent people affected by neurocysticercosis-associated epilepsy. In addition, a public consultation was conducted with experts living in endemic countries *(21)*, who live, treat and/or advocate for patients with neurocysticercosis and neurocysticercosis-associated epilepsy in the endemic countries of Brazil, Cambodia, China, Ecuador, Honduras, India, Madagascar, Mexico, Peru, Sudan and the United Republic of Tanzania.

A systematic review team, including a guideline methodologist, was commissioned to conduct systematic reviews and meta-analyses when possible of publications that addressed the PICO questions. They retrieved, critically evaluated, reviewed and synthesized relevant evidence for each question and presented their results as an evidence profile for interpretation and review by the GDG. The daily work was done by two doctoral students, closely supervised by two experts in neurocysticercosis with experience in Latin America and sub-Saharan Africa. Regular Skype meetings were held by the core group with the methodologist, and the evidence profiles were discussed and reviewed by all team members.

A multidisciplinary GDG was established, with balanced representation from all WHO regions. It included technical experts in areas such as clinical parasitology, epileptology, neurology, neurosurgery, parasitology, zoonotic diseases, public health, programme management and health-care provision. Over half of the GDG and systematic review team live in countries endemic for neurocysticercosis (Brazil, Cambodia, China, Ecuador, Honduras, India, Madagascar, Mexico, Peru, Sudan and United Republic of Tanzania) and work directly with patients as clinicians, managers

of neglected tropical disease programmes and public health specialists. As most countries in the Eastern Mediterranean Region do not have a high incidence of *T. solium*-induced disease, interest, expertise and representation of this Region were lower. The GDG examined evidence provided by the systematic review team according to the GRADE method and formulated recommendations that took into consideration benefits, harm, values, preferences, feasibility, equity, acceptability, resource requirements and other factors as appropriate. The GDG reviewed and approved the final guideline document drafted by the WHO Steering Group.

An external review group, consisting of stakeholders in diverse regions and fields, supported the guideline development by reviewing the document and providing feedback on clarity, setting specific issues and implications for implementation.

Annex 1 gives a complete list of all contributors and their affiliations and WHO region.

Management of conflicts of interests

All GDG members completed WHO declarations of interests in accordance with WHO's policy (summarized in Annex 2). Three experts declared interests that required further consideration and discussion with the Office of Compliance, Risk Management and Ethics. The review demonstrated that none of the interests presented a conflict with respect to participation in the GDG. The declarations are summarized in Annex 2.

GUIDELINE DEVELOPMENT

WHO, in collaboration with the food and agriculture organization of the united nations, the world organisation for animal health and the international livestock research institute, convened an informal consultation in Geneva on 17–18 july 2014 to build a framework for intensified control of *T. solium* taeniasis and cysticercosis and management of neurocysticercosis cases in resource-constrained endemic countries *(21)*. The consultation also initiated development of control strategies in selected countries and identified gaps in knowledge or in the availability of tools.

WHO engages with non-State actors with a significant role in global health for the advancement and promotion of public health and to encourage them to use their activities to protect and promote public health. Consultations for these guidelines were held with various groups, such as the international league against epilepsy, which completed the framework of engagement with non-State actors *(22)*, and also with other organizations such as cystinet-africa *(1)*.

Questions

In consultation and discussion with the GDG, the WHO Steering Group proposed the questions outlined below according to the PICO framework as a basis for recommendations on the diagnosis and treatment of neurocysticercosis. The questions are derived from the review and synthesis of relevant evidence to highlight gaps and identify future research needs. The questions apply to aspects of diagnosis and treatment that include the use of neuroimaging for diagnosis and case management; the role of anthelmintic, anti-inflammatory and AEDs in patients with a SEL and patients with single or multiple cerebral cysts; and treatment of patients coinfected with HIV and *T. solium*.

In addressing these questions, health providers will be guided in appropriate management of neurocysticercosis and, ultimately, improve access to and the quality of care of populations at risk.

Diagnosis

Neuroimaging with either CT scan or MRI is considered the gold standard for diagnosis of neurocysticercosis. Differences in the type and location of cysts within the brain and the model of the CT scanner may, however, affect the usefulness of these techniques. CT scan is sensitive for diagnosis of intraparenchymal neurocysticercosis but less sensitive for identifying ventricular or cisternal forms of the disease. MRI is more sensitive than CT scan, as it allows recognition of parasites and visualization of scolex, parasite degeneration, small cysts, subarachnoid cysts within the posterior fossa, spinal and basal cisterns and cysts located within the ventricles, brainstem, cerebellum and eye. Most experts agree, however, that a CT scan is more sensitive for detecting calcifications *(2, 23)*. The combination of clinical and radiological diagnosis may result in a sensitivity and a specificity of up to 99.5% and 98.9%, respectively, for a SEL *(24)*.

Serological testing of neurocysticercosis in LMICs is difficult, owing to the lack of tests, insufficient sensitivity in patients with solitary or calcified cysticerci and the requirement for neuroimaging before initiating treatment. While lentil lectin-bound glycoprotein electroimmunotransfer blot can be used as a confirmatory test for neurocysticercosis in conjunction with neuroimaging and could contribute to determining whether neuroimaging is required in areas with poor access to these facilities, a negative result in this test does not rule out neurocysticercosis, as its sensitivity is insufficient for diagnosing cases with few viable cysticerci, SEL or calcified cysticerci. Monoclonal antibody-based antigen-detecting enzyme-linked immunosorbent assays are useful for following up treatment and supporting diagnostic testing in some cases; however, their sensitivity for detecting parenchymal neurocysticercosis is limited. Treatment with anthelmintics cannot be initiated without recent neuroimaging to exclude hydrocephalus, cysts in critical locations and increased intracranial pressure, which are contraindications to anthelmintic drugs. As new serological tests are becoming available, the GDG recommended that serological testing be excluded from the guidelines and that a new review be conducted for the next update of the guidelines.

Question 1 addresses current evidence on the best neuroimaging diagnostic tool (CT scan and/or MRI) for people with neurocysticercosis.

1	For people with neurocysticercosis, is use of MRI as the first-line imaging technique more accurate for diagnosis than a CT scan?
Population	People with neurocysticercosis
Index	CT scan
Comparator or reference	MRI as the first-line diagnostic examination
Outcome	Diagnostic accuracy (frequency of detection of cases, frequency of detection of negative controls)

Treatment

Viable parenchymal cysts induce little or no brain inflammation until the cyst begins to degenerate *(25, 26)*. A significant proportion of patients with neurocysticercosis develop symptoms such as seizures due to inflammation caused by degenerating cysts in the brain and the resulting inflammatory response *(27)*. Anti-inflammatory therapy such as corticosteroids is commonly used to control inflammation *(28)*.

The current expert consensus is that anthelmintic drugs, with corticosteroids and AEDs, are beneficial in most patients with viable parenchymal cysts. The benefit of anthelmintic therapy

rather than surgical intervention or watchful waiting is unclear for ventricular, orbital and spinal neurocysticercosis. Neurological symptoms such as epileptic seizures, headaches, dizziness and vomiting are frequently reported during the initial days of anthelmintic treatment, presumably due to perilesional oedema caused by the treatment; therefore, corticosteroids should be given concomitantly. The evidence demonstrated that anthelmintic treatment reduces the number of further seizures, with generalization and relapses, and results in complete cyst resolution *(29–31)*.

Most experts agree on the effectiveness of adding corticosteroids to anthelmintic and AEDs for the treatment of viable neurocysticercosis. One trial of corticosteroids at a high dose and long duration for treatment of viable parenchymal neurocysticercosis, including multicystic disease, showed a decrease in seizures during and after treatment *(32)*. Other evidence is largely restricted to studies of patients with a SEL. Longer studies with more patients should be conducted to provide evidence for seizure control.

Questions 2 and 3 address the efficacy of the anthelmintic drugs ALB and PZQ (question 2) and of anti-inflammatory drugs (corticosteroids, question 3) in cysticidal activity and reducing seizure frequency in individuals with viable parenchymal neurocysticercosis. The usual doses are 15 mg/kg per day for ALB and 50 mg/kg per day for PZQ, divided in two to three daily doses; and the proposed length of treatment ranges from one to two weeks for parenchymal and ≥ 1 month for subarachnoid lesions *(33)*. Concomitant steroids are recommended except in very rare cases.

2	In individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
Population	Individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts
Intervention	Anthelmintic therapy (ALB, PZQ) and symptomatic treatment (anti-inflammatory and/or AEDs)
Comparator	Symptomatic treatment alone (anti-inflammatory and/or AEDs)
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

3	In individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts, is anti-inflammatory therapy associated with better clinical outcomes than either anthelmintic or AED treatment alone?
Population	Individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts
Intervention	Anti-inflammatory therapy and either anthelmintic or AED alone
Comparator	Either anthelmintic or AED treatment alone
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

The clinical symptoms of neurocysticercosis depend on the location and number of cysts, the evolutionary stage of lesions and the host immune response. A single degenerating parasite is referred to as a solitary cysticercus granuloma or a SEL and may become calcified. Children aged < 3 years usually have only one or two cysts *(34)*.

A SEL appears radiologically as a single nodular or cystic lesion with surrounding oedema with contrast enhancement. A SEL frequently resolves within 1 year of presentation, even without cysticidal drug therapy, leaving a calcified scar in approximately 20% of cases. It is not known how many patients with a SEL experience seizures; however, a long term follow-up study demonstrated increased seizure frequency in patients with associated perilesional gliosis seen on MRI *(35)*.

Question 4 addresses anthelmintic drugs (ALB or PZQ), and question 5 anti-inflammatory drugs (corticosteroids) in terms of cysticidal efficacy and reduction in seizure frequency in individuals with symptomatic neurocysticercosis with a SEL.

4	In individuals with symptomatic neurocysticercosis with a SEL, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
Population	Individuals with symptomatic neurocysticercosis with a SEL
Intervention	Anthelmintic therapy (ALB, PZQ) and symptomatic treatment alone (anti-inflammatory and/or AEDs)
Comparator	Symptomatic treatment alone (anti-inflammatory and/or AEDs)
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

5	In individuals with symptomatic neurocysticercosis with a SEL, is anti-inflammatory therapy associated with better clinical outcomes than AED treatment alone?
Population	Individuals with symptomatic neurocysticercosis with a SEL
Intervention	Anti-inflammatory therapy and AED treatment
Comparator	AED treatment alone
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse, or more frequent achievement of seizure-free status

Over time, even in the absence of treatment, *T. solium* cysts degenerate, either resolving or leaving a small calcified lesion in the parenchyma *(36)*. Brain calcifications are commonly found in patients from areas endemic for cysticercosis. In the general population, the proportion of asymptomatic individuals with calcified neurocysticercosis ranges from 5% to 25% *(2, 37–39)*. In hospital-based studies, neurocysticercosis is a primary cause of structural epilepsy in endemic areas, as the cysts can persist in the host's brain for life and have been associated with epileptic seizures and focal epilepsy. The causal factors of calcification, the pathophysiology of epileptic seizures in patients with calcified lesions and the incidence of seizure relapse in patients with calcified neurocysticercosis are poorly understood *(40)*.

AEDs are used in the treatment of epilepsy due to neurocysticercosis. Monotherapy with carbamazepine, phenobarbital or phenytoin is the common choice for seizure control *(41)* in low-resource settings, although levetiracetam is increasingly being used where it is available. A proportion of patients may require combination therapy *(42)*. Patients with epilepsy and calcified neurocysticercosis typically receive AEDs for several years and usually respond well *(40)*. Some data support withdrawal of AEDs in selected patients *(43–47)* after at least 2 years without seizures; however, some patients experience seizure relapse after discontinuation of AEDs or even refractory

epilepsy associated with hippocampal atrophy *(48)*. Further recommendations on discontinuation of AED are provided in WHO's Mental Health Gap Action Programme (mhGAP) intervention guide *(49)*.

Question 6 is whether prolonged administration of AEDs (at least 2 years) is associated with better clinical outcomes in individuals with a SEL and epilepsy than shorter regimens. While question 6 pertains to the various stages of a SEL (granuloma, calcification, lesion resolved), question 7 covers calcifications irrespective of whether they are residues from a SEL or from multiple brain cysts.

6	In individuals with a neurocysticercosis SEL and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Population	Individuals with a SEL and epilepsy
Intervention	Prolonged administration of AEDs (at least 2 years)
Comparator	Shorter regimens of AEDs (at most 2 years)
Outcome	Fewer episodes of seizure relapse or more frequent achievement of seizure-free status

7	In individuals with single or multiple calcified cysticercal lesion(s) and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Population	Individuals with calcified neurocysticercosis lesion(s) and epilepsy
Intervention	Prolonged administration of AEDs (at least 2 years)
Comparator	Shortened regimens of AEDs (at most 2 years)
Outcome	Fewer episodes of seizure relapse, or more frequent achievement of seizure-free status

Patients with neurocysticercosis may be coinfected with HIV. Pathophysiological interactions between HIV/AIDS and malaria, tuberculosis and some helminthic diseases are recognized and may also occur with neurocysticercosis *(50, 51)*. Little is known, however, about the significance of dual infection with HIV and *T. solium*.

Conversion of asymptomatic to symptomatic neurocysticercosis in individuals with HIV/AIDS has been seen after initiation of highly active antiretroviral therapy *(52)*. Thus, individuals with HIV/AIDS and asymptomatic neurocysticercosis have developed an immune reconstitution inflammatory syndrome when they started on highly active antiretroviral therapy and converted to symptomatic neurocysticercosis. There may also be interactions between antiretroviral therapy and AEDs used for neurocysticercosis, although studies on this possibility are limited, and no firm conclusions have been drawn *(53)*.

Questions 8 and 9 were intended to determine the benefit and harm of anthelmintic medications and AEDs in individuals with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal cysts (question 8) and whether increasing neurocysticercosis treatment (i.e. higher doses or longer duration of anthelmintic, anti-inflammatory or AED therapies) improves clinical outcomes in this sub-population (question 9).

8	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal cysts, which anthelmintics and AEDs are more beneficial or harmful than a placebo or control therapy?
Population	Individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable brain cysts
Intervention	Anthelmintic therapy (ALB or PZQ) and AEDs (phenobarbital, phenytoin, carbamazepine or valproic acid)
Comparator	AEDs (phenobarbital, phenytoin, carbamazepine or valproic acid)
Outcome	Seizure recurrence, adverse events

9	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal brain cysts, are higher doses and longer treatment with anthelmintics, anti-inflammatory agents and AEDs necessary for better clinical outcomes than standard neurocysticercosis treatment?
Population	Individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal cysts
Intervention	Higher doses and/or longer treatment with anthelmintics, anti-inflammatory agents and AEDs
Comparator	Standard dose and duration of treatment (anthelmintics, anti-inflammatory agents, AEDs)
Outcome	Better clinical outcomes: faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

Evidence search and retrieval

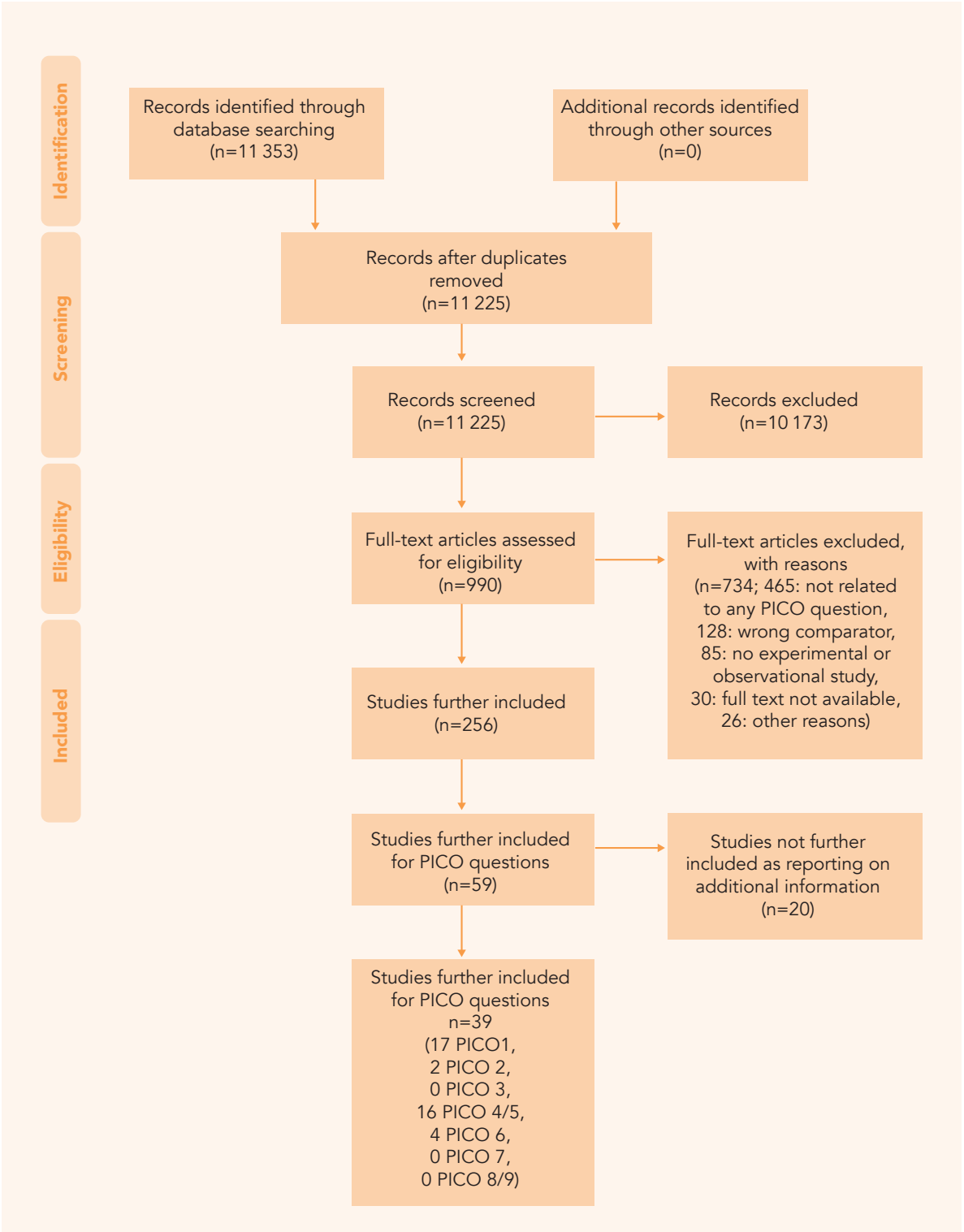
Systematic reviews and meta-analyses, where warranted, were conducted for each question according to a defined protocol developed with Cochrane methods and guidance from an external methodologist. The search strategy is summarized in Annex 3.

Two investigators retrieved, evaluated, analysed and reported the evidence. As limited literature was available, a single search strategy was used for all questions, and relevant articles were assigned to each question after a full text review. The search strategy was intended to identify all the available literature on neurocysticercosis. The investigators searched the PubMed, EMBASE, Global Index Medicus, Global Health (CABI) and Web of Science databases. Literature was screened in stages to (i) include all experimental and observational studies for diagnosis and treatment of neurocysticercosis (based on title and abstract and then on full text) and (ii) assign selected literature to the relevant question (based on full text).

When few studies were found for a question with application of strict inclusion and exclusion criteria, relevant additional studies that did not fulfil the inclusion criteria for a given question were also used. Search results by question are summarized in Fig. 3.

Data were extracted and assessed independently for bias according to the *WHO handbook for guideline development (54)* and the *Cochrane handbook for systematic reviews of interventions (55)* and synthesized into narrative reviews. Quantitative synthesis (i.e. meta-analysis) was performed when possible and appropriate. Values, preferences, feasibility and resource implications were discussed at the face-to-face guideline development meeting held in September 2017.

Fig. 3. Search strategy and results of the systematic review for all nine PICO questions



Quality assessment and grading of evidence

The GRADE system for assessing the quality of evidence and using evidence to inform decisions was applied by the GDG in drafting final recommendations. GRADE provides a framework for assessing the quality of evidence systematically *(55)* by evaluating study design, inconsistency among studies, indirectness, imprecision and publication bias (Table 1). Assessment of observational studies also includes any dose–response gradient, the direction of plausible bias and the magnitude of effect. All the evidence retrieved was evaluated in GRADE tables when possible, and GRADE tables were provided in the evidence profile. Evidence was rated as high, moderate, low or very low quality *(55)*.

Table 1. Rating of the quality of evidence in the WHO handbook for guideline development *(54)*

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Evidence for recommendations

For many of the questions, evidence was either lacking or very limited, leading to a rating of low or very low quality. See Annex 4 for the evidence profiles of each of the nine questions.

During the face-to-face meeting in September 2017, the GDG reviewed the evidence and discussed draft recommendations from the points of view of harm and benefits; quality; values, preferences and feasibility of the recommended interventions in different settings; and resource implications. In the event of disagreement, the Chair and the methodologist ascertained whether the disagreement was related primarily to the interpretation of data or to formulation of the recommendation. Draft recommendations were revised accordingly to reach consensus. As agreement was unanimous for each recommendation, a vote whereby a two-thirds majority of GDG members would be considered agreement was not required. No objections were recorded by any GDG member.

The strength of each recommendation was expressed as either:

"strong", indicating that the GDG was confident that the quality of the evidence of effect and certainty about the values, preferences, benefits and feasibility made the recommendation one that should be followed in most circumstances and settings; or

"conditional", indicating less certainty about the quality of the evidence and the values, preferences, benefits and feasibility of this recommendation and therefore circumstances or settings in which it might not apply.

RECOMMENDATION FOR DIAGNOSIS OF *T. SOLIUM* PARENCHYMAL NEUROCYSTICERCOSIS

The recommendation below reflects the discussion and conclusions of the GDG. For background information, see the respective evidence profile in Annex 4.

USE OF CT SCAN AND MRI FOR DIAGNOSIS OF NEUROCYSTICERCOSIS

RECOMMENDATION PICO 1

MRI is the tool of choice for diagnosis of neurocysticercosis, particularly when parenchymal viable, parenchymal granuloma or neurocysticercosis of the cerebellum, brain stem, ventricular, subarachnoid and spinal spaces are suspected.

CT is the tool of choice for detection of small calcified lesions.

REMARKS: CT scan should be used if MRI is unavailable or contraindicated. The benefit of the test should outweigh the risk of harm, including the risk of exposure to radiation in CT scanning and allergic reactions or renal failure due to a contrast medium.

STRENGTH OF RECOMMENDATION: Strong

CERTAINTY OF EVIDENCE: Not applicable

RATIONALE: The recommendation was considered strong as the benefits outweigh the harm due to potential inappropriate patient management and morbidity and mortality if subarachnoid or intraventricular neurocysticercosis is not diagnosed.

REMARKS: Contrast enhancement improves the diagnostic accuracy of both MRI and CT scan but is not required for the detection of calcifications.

The benefit of the test should outweigh the risk of harm, including the risk of exposure to radiation in CT scanning and allergic reactions or renal failure due to contrast medium.

RECOMMENDATIONS FOR TREATMENT OF *T. SOLIUM* PARENCHYMAL NEUROCYSTICERCOSIS

The recommendation below reflects the discussion and conclusions of the GDG. For background information, please refer to the respective evidence profiles in Annex 4.

TREATMENT OF NEUROCYSTICERCOSIS WITH ANTHELMINTICS AND ANTI-INFLAMMATORY AGENTS

Individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts (questions 2 and 3)

RECOMMENDATION (PICO 2 and 3)[a]

Anthelmintic therapy, in combination with corticosteroids, should be given to individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts to improve cyst resolution and seizure control.

Although evidence is lacking, the clinical experience of experts indicates that anthelmintic drugs should not be used in patients with numerous parenchymal cysts that are inciting inflammation and resulting in elevated intracranial pressure due to diffuse oedema or hydrocephalus. If inflammation is pronounced in these cases, patients should be treated with corticosteroids alone.

STRENGTH OF RECOMMENDATION: Strong

CERTAINTY OF EVIDENCE: Moderate (cyst resolution); moderate (seizure control)

RATIONALE: The quality of the evidence was moderate for the effect of anthelmintic therapy on cyst resolution and in improving seizure control. The GDG decided that the recommendation should be strong because the potential benefit – cyst resolution and possibly improved seizure control – probably outweighs any potential harm associated with the use of anthelmintic therapy.

[a] The search did not identify any randomized controlled trials (RCTs) in which anti-inflammatory treatment only was compared with anthelmintic and/or AEDs for neurocysticercosis with parenchymal viable lesions (PICO 3).

REMARKS: ALB in combination with corticosteroids has been shown to be superior to either corticosteroids only or no treatment. Dual therapy with PZQ and ALB with corticosteroids has been shown to be more effective than treatment with ALB alone in individuals with more than two parenchymal brain cysts *(56)*.

There were no relevant studies in which the effect of ALB was compared with that of PZQ in combination with corticosteroids in the treatment of symptomatic neurocysticercosis and viable parenchymal brain cysts.

Evidence on the use of ALB in pregnant women was not evaluated. Pregnant women should seek expert advice before receiving treatment with ALB. There is no evidence that anthelmintic therapy in children should be different from that in adults; however, no solid conclusions can be drawn for this patient population from the RCTs examined, as none or too few children were included. Carpio et al. *(57)* included a total of 15 children (eight given ALB and seven given placebo), while Garcia et al. *(56)* included none.

Longer dosing with corticosteroids (i.e. 28 days) was associated with better clinical outcomes than shorter schedules (e.g. 10 days) *(32)*.

Individuals with symptomatic neurocysticercosis and a SEL (questions 4 and 5)

RECOMMENDATION PICO 4 and 5

ALB and corticosteroids should be given to individuals with symptomatic neurocysticercosis and a SEL for better cyst resolution and potentially improved seizure control.

Strength of recommendation: Conditional

CERTAINTY OF EVIDENCE: Low (for PICO 4 cyst resolution) to very low (for seizure control); moderate (for PICO 5)

RATIONALE: The quality of the evidence was considered low for the effect of anthelmintic therapy plus corticosteroids on cyst resolution and very low for the effect of improving seizure control.

The GDG decided that the recommendation should be a conditional because of methodological heterogeneity among the studies; however, all the studies found that the combination of ALB and corticosteroids was beneficial.

REMARKS: The quality of the evidence was graded as low for the effect of anthelmintic therapy on cyst resolution and very low for the effect of anthelmintic therapy on seizure control in individuals with symptomatic neurocysticercosis with a SEL.

The evidence for treatment with corticosteroids alone in individuals with symptomatic neurocysticercosis with a SEL was graded as moderate, as it was downgraded for indirectness.

Many studies were available on the use of anthelmintic therapy in combination with corticosteroids in individuals with a SEL, but significant limitations were found in synthesizing the data for meta-analyses.

TREATMENT OF NEUROCYSTICERCOSIS AND EPILEPSY WITH ANTIEPILEPTIC DRUGS

In individuals with a SEL and epilepsy

RECOMMENDATION PICO 6

Withdrawal of AEDs should be considered 6 months after the last seizure in individuals with a SEL and epilepsy and a low risk of seizure recurrence (defined as patients with a resolved granuloma, no residual calcification and who are seizure free).

AED therapy should be continued in people with a SEL that persists on neuroimaging and those that resolve with residual calcification.

REMARKS: There is limited evidence on the optimal duration of AED therapy for a SEL; however, it appears to be a few weeks after complete resolution of the SEL.

STRENGTH OF RECOMMENDATION: Conditional

CERTAINTY OF EVIDENCE: Moderate to low[a]

RATIONALE: The recommendation is conditional because limited evidence was available. Nevertheless, the morbidity and cost associated with continuing AED treatment in patients with no risk factors for seizure recurrence (i.e. patients with a resolved granuloma, no residual calcification and who have been seizure free for at least 3 months) in resource-limited settings outweighs the benefit of continuing AED therapy.

[a] The quality of the evidence was graded as low for seizure recurrence within 6 months of stopping AEDs as compared with 12–24 months and 6–12 months as compared with 24 months of stopping AED treatment, whereas the evidence was graded as moderate for seizure recurrence for 6 months as compared with 24 months of AED treatment in individuals with a SEL neurocysticercosis whose cysts had calcified.

REMARKS: Many factors influence seizure recurrence in patients with epilepsy. For other considerations in managing epilepsy, see the WHO guidelines on epilepsy management *(58)*.

No studies were available on SELs and shortened AED therapy in countries other than India; however, anecdotal data from Latin America support the published findings.

In individuals with a calcified lesion and epilepsy

RECOMMENDATION PICO 7

AED therapy should be continued for at least 2 years in people with single or multiple calcified neurocysticercosis and epilepsy. These patients should be closely monitored if treatment is withdrawn.

STRENGTH OF RECOMMENDATION: Conditional

CERTAINTY OF EVIDENCE: Very low

RATIONALE: The recommendation is conditional because the panel considered that the effect was great enough, given the limited evidence available.

REMARKS: Many factors influence seizure recurrence in patients with epilepsy. For other considerations in managing epilepsy, see the WHO guidelines on epilepsy management *(58)*.

TREATMENT OF NEUROCYSTICERCOSIS IN IMMUNOCOMPROMISED PATIENTS

RECOMMENDATION PICO 8 and 9

Patients with neurocysticercosis who are coinfected with HIV should be treated according to the guidelines for treating patients with neurocysticercosis without HIV/AIDS.

STRENGTH OF RECOMMENDATION: Conditional

CERTAINTY OF EVIDENCE: Very low

RATIONALE: The recommendation is conditional because of the lack of evidence on treating patients with neurocysticercosis who are coinfected with HIV.

REMARKS: Only case reports were available on the potential association between immune reconstitution inflammatory syndrome and neurocysticercosis in patients with neurocysticercosis who begin antiretroviral therapy for HIV/AIDS. Caution should therefore be used when initiating therapy in patients coinfected with neurocysticercosis and HIV. Treatment of patients with neurocysticercosis and HIV/AIDS should be in accordance with the WHO guidelines on treatment of HIV/AIDS *(59)*.

AED treatment of neurocysticercosis should be provided according to the *WHO mhGAP guideline (2015) update (60)*.

RESEARCH PRIORITIES

The extensive search for evidence on the diagnosis and treatment of neurocysticercosis yielded useful baseline information but also highlighted significant gaps. The GDG identified priority areas for research to increase certainty about the most effective interventions for diagnosis and treatment of neurocysticercosis. Establishment of research networks with a focus on LMICs is encouraged.

DIAGNOSIS OF PARENCHYMAL NEUROCYSTICERCOSIS

The GDG calls upon the research community to conduct further research to answer the following questions.

- How can access to neuroimaging facilities (CT scan, MRI) be increased for populations at risk of neurocysticercosis and other neurological diseases?
- How can serology be used to advocate for better access to neuroimaging and neuroimaging-based treatment?
- How can serology be used to identify populations that might benefit from interventions to control or interrupt transmission of taeniasis?
- Could a rapid point-of-care serological test (e.g. antibody and/or antigen test) to detect (neuro)cysticercosis be developed for use in resource-poor settings for direct diagnosis or screening?
- Is the diagnostic value of serology (specifically, antibody response) in patients coinfected with neurocysticercosis and HIV/AIDS similar to that in patients with neurocysticercosis only?

TREATMENT OF PARENCHYMAL NEUROCYSTICERCOSIS

The GDG calls upon the research community to conduct further research to answer the following questions.

- What constitutes optimal anthelmintic therapy (PZQ, ALB) in terms of dose and treatment length?
- What are the effects of antiparasitic therapy and anti-inflammatory therapy on the development of calcifications? What is the optimal dose and duration of anti-inflammatory therapy (corticosteroids) for individuals with symptomatic neurocysticercosis?
- Does anthelmintic therapy in combination with corticosteroids contribute to resolving seizures, i.e. reducing their severity and frequency and/or reducing the duration of AED therapy?
- What are the effects of antiparasitic therapy on development of calcifications and chronic (> 2 years) epilepsy, as calcifications are a risk factor for seizures?
- What are the optimal drug(s), dose and duration of AED therapy for neurocysticercosis?
- Could additional strong evidence be obtained to allow recommendation of the use of anthelmintic and anti-inflammatory therapy in individuals with symptomatic neurocysticercosis and SEL?

- What are the optimal treatment and/or special considerations for patients coinfected with neurocysticercosis and HIV/AIDS who are at risk of immune reconstitution inflammatory syndrome?
- What is the role of serology in areas with poor access to neuroimaging in improving management (treatment follow-up) of patients with neurocysticercosis?

THE GUIDELINES

MAIN POINTS

- The guidelines will be available on the WHO website.
- Capacity-building will be conducted online and in regional workshops.
- Countries are encouraged to adapt the guidelines at national level and for field use.
- Inclusion of the guidelines in research projects is encouraged.
- The guidelines will be reviewed in 3–5 years.

DISSEMINATION

These recommendations will provide guidance on the diagnosis and management of *T. solium* neurocysticercosis. They will be made available for downloading on the WHO website and widely disseminated through WHO regional and country offices, collaborating centres, professional organizations and partner agencies. Capacity-building will be undertaken on web-based platforms and in regional workshops.

IMPLEMENTATION

WHO publications and training and clinical management manuals will be revised to reflect the updated recommendations. Countries are encouraged to adapt their national guidance documents accordingly.

The guidelines can be adapted for field use by developing training materials in consultation with regional, national and local stakeholders. Adaptations should include translation into appropriate languages and should ensure that the interventions are acceptable in local sociocultural contexts and health systems and also respect gender, equity and human rights. The guidelines will also be useful for academics and researchers for teaching, research and planning research networks.

UPDATING

The guidelines are expected to be reviewed in 3–5 years. New evidence will be monitored regularly by the departments of Control of Neglected Tropical Diseases and Mental Health and Substance Use. Should there be significant changes in practice and/or the evidence base that affect any of the recommendations, a review may be undertaken earlier.

REFERENCES

1. CYSTINET-Africa. 2021 (https://www.cysti.net/, accessed 23 March 2021).

2. Sánchez AL, Lindbäck J, Schantz PM, Sone M, Sakai H, Medina MT et al. A population-based, case-control study of *Taenia solium* taeniasis and cysticercosis. Ann Trop Med Parasitol. 1999;93(3):247–58.

3. Disease and Injury Incidence and Prevalence Collaborators. Global, regional and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211–59.

4. Torgerson PR, Devleesschauwer B, Praet N, Speybroeck N, Willingham AL, Kasuga F et al. World Health Organization estimates of the global and regional disease burden of 11 foodborne parasitic diseases, 2010: A data synthesis. PLoS Med. 2015;12(12):e1001920.

5. Winkler AS, Willingham AL 3rd, Sikasunge CS, Schmutzhard E. Epilepsy and neurocysticercosis in sub-Saharan Africa. Wien Klin Wochenschr. 2009;12(Suppl 3):3–12.

6. Sibat HF, editor. Novel aspects on cysticercosis and neurocysticercosis. London: Intech Open; 2013.

7. Winkler AS, Richter H. Landscape analysis: management of neurocysticercosis with an emphasis on low- and middle-income countries. Washington (DC): Pan American Health Organization; 2015.

8. Guideline for preventive chemotherapy for the control of *Taenia solium* taeniasis. Washington (DC): World Health Organization Regional Office for the Americas/Pan American Health Organization; 2021 [in press].

9. Donadeu M, Lightowlers MW, Fahrion AS, Kessels J, Abela-Ridder B. *Taenia solium*: WHO endemicity map update. Wkly Epidemiol Rec. 2016;91(49–50):595–9.

10. Carabin H, Ndimubanzi PC, Budke CM, Nguyen H, Qian Y, Cowan LD et al. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Negl Trop Dis. 2011;5(5):e1152.

11. Neurological Disorders Collaborator Group. Global, regional and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 2017;16(11):877–97.

12. Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 2014;37:59–70.

13. Epilepsy fact sheet. Geneva: World Health Organization; 2019 (https://www.who.int/en/news-room/fact-sheets/detail/epilepsy, accessed 6 October 2020).

14. Medina MT, Rosas E, Rubio-Donnadieu F, Sotelo J. Neurocysticercosis as the main cause of late-onset epilepsy in Mexico. Arch Intern Med. 1990;150(2):325–7.

15. Medina MT, Durón RM, Martínez L, Osorio JR, Estrada AL, Zúniga C et al. Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salamá Study. Epilepsia, 2005;46(1):124–31.

16. Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases. Geneva: World Health Organization; 2010.

17. Winkler AS, Klohe K, Schmidt V, Haavardsson I, Abraham A, Prodjinotho UF et al. Neglected tropical diseases – the present and the future. Tidsskr Nor Laegefor. 2018;138(3):10.4045.

18. Poudel I, Sah K, Subedi S, Kumar Singh D, Kushwaha P, Colston A et al. Implementation of a practical and effective pilot intervention against transmission of *Taenia solium* by pigs in the Banke district of Nepal. PLoS Negl Trop Dis. 2019;13(2):e0006838.

19. Gauci C, Jayashi C, Lightowlers MW. Vaccine development against the *Taenia solium* parasite: the role of recombinant protein expression in *Escherichia coli*. Bioengineered. 2013;4(5):343–7.

20. Medina MT, Aguilar-Estrada RL, Alvarez A, Durón RM, Martínez L, Dubón S et al. Reduction in rate of epilepsy from neurocysticercosis by community interventions: the Salamá, Honduras study. Epilepsia. 2011;52(6):1177–85.

21. Public consultation of experts to join the Guideline Development Group (GDG) for diagnosis and treatment guidelines for *Taenia solium* neurocysticercosis. Geneva: World Health Organization; 2015.

22. WHO's engagement with non-State actors. Geneva: World Health Organization; 2021 (https://www.who.int/about/partnerships/non-state-actors, accessed 23 March 2021).

23. Garcia HH, Del Brutto OH. Imaging findings in neurocysticercosis. Acta Trop. 2003;87(1):71–8.

24. Rajshekhar V, Chandy MJ. Validation of diagnostic criteria for solitary cerebral cysticercus granuloma in patients presenting with seizures. Acta Neurol Scand. 1997;96(2):76–81.

25. Singhi P. Neurocysticercosis. Ther Adv Neurol Disord. 2011;4(2):67–81.

26. Singh SK, Prasad KN. Immunopathogenesis of neurocysticercosis: role of cytokines. Immunome Res. 2015;11(2):1.

27. Del Brutto OH, Sotelo J. Neurocysticercosis: an update. Rev Infect Dis. 1988;10(6):1075–87.

28. Jung H, Hurtado M, Medina MT, Sanchez M, Sotelo J. Dexamethasone increases plasma levels of albendazole. J Neurol. 1990;237(5):279–80.

29. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med. 2004;350(3):249–58.

30. Vazquez V, Sotelo J. The course of seizures after treatment for cerebral cysticercosis. N Engl J Med. 1992;327(10):696–701.

31. Medina MT, Genton P, Montoya MC, Córdova S, Dravet C, Sotelo J. Effect of anticysticercal treatment on the prognosis of epilepsy in neurocysticercosis: a pilot trial. Epilepsia. 1993;34(6):1024–7.

32. Garcia HH, Gonzales I, Lescano AG, Bustos JA, Pretell EJ, Saavedra H et al. Enhanced steroid dosing reduces seizures during antiparasitic treatment for cysticercosis and early after. Epilepsia. 2014;55(9):1452–9.

33. White AC Jr, Coyle CM, Rajshekar V, Singh G, Hauser WA, Mohanty A et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2018;66(8):e49–75.

34. Del Brutto OH. Neurocysticercosis in infants and toddlers: report of seven cases and review of published patients. Pediatr Neurol. 2013;48(6):432–5.

35. de Souza A, Nalini A, Kovoor JM, Yeshraj G, Siddalingaiah HS, Thennarasu K. Perilesional gliosis around solitary cerebral parenchymal cysticerci and long-term seizure outcome: a prospective study using serial magnetization transfer imaging. Epilepsia. 2011;52(10):1918–27.

36. Escobar A. The pathology of neurocysticercosis. In: Palacios E, Rodriquez-Carbajal J, Taveras JM, editors. Cysticercosis of the central nervous system. Springfield (IL): Charles C. Thomas; 1983:27–54.

37. Fleury A, Gomez T, Alvarez I, Meza D, Huerta M, Chavarria A et al. High prevalence of calcified silent neurocysticercosis in a rural village of Mexico. Neuroepidemiology. 2003;22(2):139–45.

38. Moyano LM, O'Neal SE, Ayvar V, Gonzalvez G, Gamboa R, Vilchez P et al. High prevalence of asymptomatic neurocysticercosis in an endemic rural community in Peru. PLoS Negl Trop Dis. 2016;10(12):e0005130.

39. Del Brutto OH, Issa NP, Salgado P, Del Brutto VJ, Zambrano M, Lama J et al. The association between neurocysticercosis and hippocampal atrophy is related to age. Am J Trop Med Hyg. 2017;96(1):243–8.

40. Nash TE, Del Brutto OH, Butman JA, Corona T, Delgado-Escueta A, Duron RM et al. Calcific neurocysticercosis and epileptogenesis. Neurology. 2004;62(11):1934–8.

41. Blocher J, Schmutzhard E, Wilkins PP, Gupton PN, Schaffert M, Auer H et al. A cross-sectional study of people with epilepsy and neurocysticercosis in Tanzania: clinical characteristics and diagnostic approaches. PLoS Negl Trop Dis. 2011;5(6):e1185.

42. Rajshekhar V, Jeyaseelan L. Seizure outcome in patients with a solitary cerebral cysticercus granuloma. Neurology. 2004;62(12):2236–40.

43. Sharma M, Singh T, Mathew A. Antiepileptic drugs for seizure control in people with neurocysticercosis. Cochrane Database Syst Rev. 2015;(10):CD009027.

44. Thussu A, Arora A, Prabhakar S, Lal V, Sawhney IM. Acute symptomatic seizures due to single CT lesions: how long to treat with antiepileptic drugs? Neurol India. 2002;50(2):141–4.

45. Gupta M, Agarwal P, Khwaja GA, Chowdhury D, Sharma B, Bansal J et al. Randomized prospective study of outcome of short term antiepileptic treatment in small single enhancing CT lesion in brain. Neurol India. 2002;50(2):145–7.

46. Singhi PD, Dinakaran J, Khandelwal N, Singhi SC. One vs. two years of anti-epileptic therapy in children with single small enhancing CT lesions. J Trop Pediatr. 2003;49(5):274–8.

47. Verma A, Misra S. Outcome of short-term antiepileptic treatment in patients with solitary cerebral cysticercus granuloma. Acta Neurol Scand. 2006;113(3):174–7.

48. Jama-António JMC, Yasuda CL, Cendes F. Neurocysticercosis and hippocampal atrophy: MRI findings and the evolution of viable or calcified cysts in patients with neurocysticercosis. Front Neurol. 2019;10:449.

49. mhGAP intervention guide. Mental Health Gap Action Programme Version 2.0 for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/250239, accessed 23 March 2021).

50. Kroidl I, Saathoff E, Maganga L, Makunde WH, Hoerauf A, Geldmacher C et al. Effect of *Wuchereria bancrofti* infection on HIV incidence in southwest Tanzania: a prospective cohort study. Lancet. 2016;388(10054):1912–20.

51. Landscape analysis: management of neurocysticercosis with an emphasis on low- and middle-income countries. Geneva: World Health Organization; 2015.

52. Serpa JA, Moran A, Goodman JC, Giordano TP, White AC Jr. Neurocysticercosis in the HIV era: a case report and review of the literature. Am J Trop Med Hyg. 2007;77(1):113–7.

53. Bhigjee AI, Rosemberg S. Optimizing therapy of seizures in patients with HIV and cysticercosis. Neurology. 2006;67(12 Suppl 4):S19–22.

54. WHO handbook for guideline development, second ed. Geneva: World Health Organization; 2014.

55. Higgins J, Thomas J. Cochrane handbook for systematic reviews of interventions. Oxford: Cochrane Training; 2021 (https://training.cochrane.org/handbook/current, accessed 23 March 2021).

56. Garcia HH, Gonzales I, Lescano AG, Bustos JA, Zimic M, Escalante D et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. Lancet Infect Dis. 2014;14(8):687–95.

57. Carpio A, Kelvin EA, Bagiella E, Leslie D, Leon P, Andrews H et al. Effects of albendazole treatment on neurocysticercosis: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2008;79(9):1050–5.

58. Epilepsy and seizures. Evidence-based recommendations for management of epilepsy and seizures in non-specialized health settings. Geneva: World Health Organization; 2021.

59. Update of recommendations on first- and second-line antiretroviral regimens. Policy brief. Geneva: World Health Organization; 2019 (https://www.who.int/publications/i/item/WHO-CDS-HIV-19.15, accessed 22 July 2021)

60. EPI 4: Antiepileptic medications for adults and children with HIV [new 2015]. Geneva: World Health Organization; 2015 (https://www.who.int/mental_health/mhgap/evidence/resource/epilepsy_q14.pdf, accessed June 2021).

ANNEX 1
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ANNEX 2
DECLARATIONS OF INTERESTS

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Professor Xiao Nong Zhou	Chinese Center for Disease Control and Prevention, Shanghai, China.	None declared	

ANNEX 3
SYSTEMATIC REVIEW SEARCH STRATEGY

The systematic reviews were conducted by Annette Abraham and Javier Bustos, supported by Hélène Carabin and with oversight from Hector Garcia and Andrea Sylvia Winkler over the course of three years (2016–2019). All members of the systematic review team are knowledgeable in the field of *T. solium* (neuro)cysticercosis/taeniasis and have studied the parasite in endemic countries in various large-scale projects.

Five databases were searched: PubMed, EMBASE, Global Index Medicus, Global Health (CABI) and Web of Science (Table A3.1). No time or language restrictions were applied.

When few studies were available with application of strict inclusion and exclusion criteria, highly relevant additional studies that did not fulfil the inclusion criteria for a given question were included from the full search.

Table A3.1. Search terms and results by database

Database and search terms	No. of results
PubMed (http://www.pubmed.gov)	
("Neurocysticercosis" [Mesh] OR Neurocysticercos* [TW]) OR ((brain[TW] OR cerebral [TW] OR "Central Nervous System"[TW] OR "Central Nervous"[TW] OR CNS[TW] OR neuro[TW] OR intramedullary[TW] OR extramedullary[TW] OR medullary[TW] OR ventricular[TW] OR subarachnoid*[TW] OR spinal[TW] OR intraparenchymal[TW] OR extraparenchymal[TW] OR parenchymal[TW] OR intraventricular[TW] OR subarachnoid[TW] OR calcified[TW] OR viable[TW] OR "single enhancing"[TW] OR active[TW] OR inactive[TW] OR headache*[TW] OR "intracranial hypertension" [TW] OR "neurological symptoms" [TW] OR epilepsy [TW] OR "seizures" [MH] OR seizure* [TW] OR "intracranial pressure"[TW]) AND (CYSTICERC* [TW] OR "CYSTICERCOSIS" [MH] OR "brain cysts" [TW] OR "brain cyst" [TW])) NOT ("Animals" [MH] NOT (HUMANS [MH] AND Animals [MH]))	4121
EMBASE (http://www.embase.com)	
"neurocysticercosis"/exp OR Neurocysticercos*:ti,ab,de OR ((brain:ti,ab,de OR cerebral:ti,ab,de OR "Central Nervous":ti,ab,de OR CNS:ti,ab,de OR neuro:ti,ab,de OR intramedullary:ti,ab,de OR extramedullary:ti,ab,de OR medullary:ti,ab,de OR ventricular:ti,ab,de OR subarachnoid*:ti,ab,de OR spinal:ti,ab,de OR intraparenchymal:ti,ab,de OR extraparenchymal:ti,ab,de OR parenchymal:ti,ab,de OR intraventricular:ti,ab,de OR subarachnoid:ti,ab,de OR calcified:ti,ab,de OR viable:ti,ab,de OR "single enhancing ":ti,ab,de OR active:ti,ab,de OR inactive:ti,ab,de OR headache*:ti,ab,de OR "intracranial hypertension ":ti,ab,de OR "neurological symptoms":ti,ab,de OR epilepsy:ti,ab,de OR "seizure"/exp OR seizure*:ti,ab,de OR "intracranial pressure ":ti,de,ab) AND (CYSTICERC*:ti,ab,de OR "cysticercosis"/exp OR "brain cysts":ti,ab,de OR "brain cyst":ti,ab,de)) AND embase/lim	7239

Global Index Medicus http://www.globalhealthlibrary.net/ limited to Regional Databases LILACS, AIM, WPRIM; IMSEAR, IMEMR	
(mh:(Neurocysticercosis)) OR Neurocysticercos* OR neurocisticercos* OR ((brain OR cerebral OR (Central Nervous) OR CNS OR neuro OR intramedullary OR extramedullary OR medullary OR ventricular OR subarachnoid* OR spinal OR intraparenchymal OR extraparenchymal OR parenchymal OR intraventricular OR subarachnoid OR calcified OR viable OR (single enhancing) OR active OR inactive OR headache* OR (intracranial hypertension) OR (neurological symptoms) OR epilepsy OR seizure* OR (intracranial pressure)) AND (CYSTICERC* OR "brain cysts" OR (brain cyst)))	1394
Global Health (CABI) https://www.cabdirect.org/	
Neurocysticercosis OR (((brain OR cerebral OR "Central Nervous System" OR "Central Nervous" OR CNSOR neuro OR intramedullary OR extramedullary OR medullary OR ventricular OR subarachnoid* OR spinal OR intraparenchymal OR extraparenchymal OR parenchymal OR intraventricular OR subarachnoid OR calcified OR viable OR "single enhancing" OR active OR inactive OR headache* OR "intracranial hypertension" OR "neurological symptoms" OR epilepsy OR seizure* OR "intracranial pressure") AND (CYSTICERC* OR "brain cysts" OR "brain cyst")))	2322
Web of Science (Emerging Sources Citation Index (ESCI) - 2015-present) http://apps.webofknowledge.com/	
neurocysticercosis OR (((brain OR cerebral OR "Central Nervous System" OR "Central Nervous" OR CNSOR neuro OR intramedullary OR extramedullary OR medullary OR ventricular OR subarachnoid* OR spinal OR intraparenchymal OR extraparenchymal OR parenchymal OR intraventricular OR subarachnoid OR calcified OR viable OR "single enhancing" OR active OR inactive OR headache* OR "intracranial hypertension" OR "neurological symptoms" OR epilepsy OR seizure* OR "intracranial pressure") AND (CYSTICERC* OR "brain cysts" OR "brain cyst")))	28

ANNEX 4
EVIDENCE PROFILES

EVIDENCE PROFILE: QUESTION 1

1	For people with neurocysticercosis, is use of MRI as the first-line imaging technique more accurate for diagnosis than a CT scan?
Population	People with neurocysticercosis
Index	CT scan
Comparator or reference	MRI
Outcome	Diagnostic accuracy (frequency of detection of cases, frequency of detection of negative controls)

Background

Neurocysticercosis is defined as infection of the central nervous system by the metacestode larval stage of the zoonotic tapeworm *T. solium*. Neurocysticercosis remains a major challenge to public health because of the associated secondary epilepsy and other neurological symptoms *(1–3)*. *T. solium* larvae usually establish themselves in the brain parenchyma as viable cysts, although they also sometimes establish themselves elsewhere in the brain or spine, such as the extraparenchymal, subarachnoid or ventricular space *(4)*. During their natural life cycle or after anthelmintic treatment, these cysts degenerate, either resolving or leaving a small calcified lesion in the parenchyma.

Neurocysticercosis is diagnosed mainly by neuroimaging, by either CT scan or MRI. The sensitivity of cyst detection by CT scan is sufficient for intraparenchymal neurocysticercosis but is lower for ventricular or cisternal forms of the disease. MRI is more sensitive than CT scan for detection of cases, as it allows better recognition of viable parasites, parasite degeneration, small cysts, racemose cysts within the posterior fossae, spinal and basal cisterns and cysts located within the ventricles, brainstem, cerebellum and eye. Most experts agree, however, that CT scanning is more sensitive for detection of calcifications *(5)*.

The aim of the systematic review was to evaluate current evidence for selecting the best neuroimaging diagnostic tool (CT scan and/or MRI) for people with neurocysticercosis.

Inclusion and exclusion criteria

The search strategy and results are given in Annex 3 and Guideline development: evidence search and retrieval (Fig. 3), respectively.

INCLUSION CRITERIA	
Types of studies:	Experimental, observational and case series that comprised more than three cases. In this review, the smallest case series comprised eight patients.
Types of participants:	Individuals with neurocysticercosis on CT scan and MRI
Types of diagnostic tool:	MRI and CT scan
Types of outcome measures:	Frequency of detection of cases and of negative controls. The frequency of detection of cases is calculated in relation to the total number of cases detected by any of the imaging methods, as the best possible estimation for the sensitivity of the examination.
Exclusion criteria:	Case reports

Summary of findings

Seventeen studies were identified in which the performance of MRI and/or of CT scan for the diagnosis of neurocysticercosis was evaluated systematically (Table A4.1.1). Most of the studies involved few patients and were descriptive, retrospective or case series. In 15 of the 17 studies, comparison of findings with CT scan and with MRI was not blinded or performed by independent readers. Additionally, contrast enhancement was seldom systematically used, reported or analysed. Another potential limitation is the evolving quality of neuroimaging. The increasing availability of more sophisticated, accurate CT scanners and MRI machines in recent years may invalidate pooling of the results of these studies.

MRI and CT scan were compared for the most common presentations of neurocysticercosis: parenchymal (viable, granuloma and calcification, summarized in Tables A4.1.2, A4.1.3 and A4.1.4, respectively), subarachnoidal, ventricular (Table A4.1.5) and spinal forms.

Table A4.1.1. Summary of included studies and main findings for question 1

Ref.	Study design	Age (range)	No. of patients	Neurocysti-cercosis diagnostic	CT scan	MRI	Blinded readings	Comparable findings[a] (when available)
6	Prospective cohort	1–16 years	115	Neuroimaging and symptoms	115	75	NR	P. viable cysts: CT=20; MRI=20
7	Retrospective case series	2–80 years	21[b]	Neuroimaging and pathology	21	21	Yes	Ventricular cyst: CT=0; MRI=1
8	Retrospective case series	14– 71 years	30	Neuroimaging, symptoms and CSF and serum assay	30	30	NR	Ventricular cysts: CT=3; MRI=30

9	Retrospective case series	6 months–16 years	54	Neuroimaging	54	8	NR	P. viable cysts: CT=6; MRI=6 P. calcifications: CT=2; MRI=0
10	Community-based cross-sectional	≥ 60 years	248	Neuroimaging	248	248	NR	P. viable cysts: CT=2; MRI=2 P. calcifications: CT=28; MRI=18
11	Prospective cohort	8–38 years	77	Neuroimaging	77	9	NR	P. viable cysts: CT=0; MRI=2
12	Clinical trial	22–65 years	36	Neuroimaging and immunoassay	36	36	NR	Ventricular cysts: CT=6; MRI=8
13	Prospective case series	15–45 years	11	Neuroimaging and pathology	11	11	Yes	Ventricular cysts: CT=0; MRI=11
14	Retrospective case series	6– 65 years	56	Neuroimaging	40	56	NR	Ventricular cysts: CT=0; MRI=11 P. calcifications: CT=13; MRI=5
15	Retrospec-tive case series	4– 66 years	35	Neuroimaging	35	6	NR	P. granulomas: CT=0; MRI=3
16	Prospective case series	2–50 years	672	Neuroimaging and CSF and serum immunoassay	67	67	NR	P. granulomas: CT=67[c]; MRI=12
17	Retrospective case series	NR	16	Neuroimaging (spontaneous lesion resolution or after ALB) and pathology	16	16	NR	P. granulomas: CT=15; MRI=16
18	Prospective case series	NR	35	Neuroimaging	35	35	NR	P. calcifications: CT=52; MRI=52
19	Prospective cohort	6–72 years	86	Del Brutto's criteria (including neuroimaging)	86	86	NR	P. granulomas: CT=56; MRI=91[d]
20	Retrospective case series	17–63 years	8	Neuroimaging, symptoms, and CSF and serum immunoassay	8	8	NR	P. viable cysts: CT=2; MRI=3 P. calcifications: CT=5; MRI=1
21	Retrospective case series	7–69 years	26	Neuroimaging and pathology and/or CSF immunoassay	10	26	NR	Ventricular cysts: CT=0; MRI=6 P. calcifications: CT=7; MRI=3

22	Prospective case series	12–47 years	50	Neuroimaging, symptoms and immunoassay	50	50	NR	P. calcifications: CT=12; MRI=6

ALB: albendazole; CSF: cerebrospinal fluid; CT: computerized tomography; MRI: magnetic resonance imaging; NR: not reported; P.: parenchymal

[a] Numbers of CT scans and MRIs conducted for the same participants for comparison

[b] Only three lesions were ventricular neurocysticercosis.

[c] Undefined granulomas (not confirmed as neurocysticercosis)

[d] After contrast injection, CT scan detected 86 granulomas and MRI detected 101 granulomas.

Parenchymal viable cysts

In a case series of eight patients, Suss et al. *(20)* found that CT scan identified three viable cysts in two patients, while MRI detected those three cysts and two additional lesions (one additional cyst in a patient with a cyst identified by CT scan and one cyst in a patient with no cyst identified on CT scan. In a retrospective case-series study of six patients, Del Brutto et al. *(9)* found that MRI and CT scan performed similarly in identifying intraparenchymal viable cysts. In a prospective cohort study, Aguilar Rebolledo et al. *(6)* identified viable cysts with both MRI and CT scan in 20 of 75 children who received both examinations, with an agreement of 100% (Kappa 1). In a retrospective study of patients with epilepsy, Garg et al. *(11)* found that MRI identified single cystic lesions in two of nine patients presenting with a normal CT scan. In a community-based prospective study, Del Brutto et al. *(10)* found that MRI and CT scans performed equally (i.e. two cases of neurocysticercosis were identified with both methods from a pool of 248 CT scan and MRI examinations).

Table A4.1.2. Frequencies of detection of cases and negative controls by MRI and CT scan in patients with parenchymal vesicular neurocysticercosis

Reference	Frequency of detection (cases)		Frequency of detection (negatives)	
	MRI	CT scan	MRI	CT scan
20	100% (3/3)	66.7% (2/3)	100% (5/5)	100% (5/5)
6	100% (20/20)	100% (20/20)	100% (55/55)	100% (55/55)
9	100% (6/6)	100% (6/6)	100% (2/2)	100% (2/2)
11	100% (2/2)	0% (0/2)	100% (7/7)	100% (7/7)
10	100% (2/2)	100% (2/2)	100% (246/246)	100% (246/246)

Patients with vesicular neurocysticercosis were defined as those with a positive MRI and/or CT scan for parenchymal vesicular lesions. Patients without vesicular cysts were defined as those with a negative MRI and CT scan for parenchymal vesicular lesions.

Parenchymal granulomas

In a cross-sectional study involving 67 patients presenting with a CT contrast-enhancing ring or disc lesions and epilepsy *(16)*, neurocysticercosis was diagnosed in only 12 by MRI. The diagnosis was based on the presence of a mural nodule in a cyst on neuroimaging and a positive cysticercosis enzyme-linked immunosorbent assay on cerebrospinal fluid cysticercal antibody. Morgado et al. *(15)* presented a retrospective case series in which nodular enhancing lesions were found on MRI in two patients with oedema only on CT scan. Rajshekhar et al. *(17)* reported a case

series of 16 patients with solitary cysticercus granuloma on CT scan or MRI. CT scan with contrast allowed identification of cysts in 15 of 16 patients; however, all lesions were visible on CT scan when thinner sections were examined. MRI without contrast was positive in 15 of 16 patients, and the remaining granulomas were visible after use of contrast. Aguilar Rebolledo et al. *(6)* found an agreement of 88% (Kappa 0.77) in a cohort of children, favouring MRI; however, no numbers were provided except the Kappa index. In a study involving 86 patients with a solitary cysticercus and seizures diagnosed by contrast-enhanced MRI and CT scan, Souza et al. *(19)* found that MRI was more sensitive than plain CT scan in detecting cysticercal lesions ($P = 0.003$), but there was no statistically significant difference between contrast CT scan and MRI. Lesions were identified in only 56 patients by non-contrast CT, while all cases were identified by contrast CT scan and by MRI.

Table A4.1.3. Frequencies of detection of cases and negative controls by MRI and CT scan scan in patients with parenchymal granuloma neurocysticercosis

Reference	Frequency of detection (cases)		Frequency of detection (negatives)	
	MRI	CT scan scan	MRI	CT scan
16	100% (12/12)	NA[a]	100% (55/55)	NA[a]
15	100% (3/3)	0% (0/3)	–	–
17	93.8% (15/16)[b]	93.8% (15/16)[c]	–	–
19[d]	95.09% (97/102)	54.9% (56/102)	–	–

Patients with granuloma neurocysticercosis were defined as those with a positive MRI and/or CT for parenchymal single cysticercus granuloma. Patients without granuloma neurocysticercosis were defined as those with MRI and CT scans negative for parenchymal single cysticercus granuloma.

NA: data not available

[a] All 67 patients were identified by CT scan; details were not provided.

[b] MRI without contrast. After contrast enhancement, all 16 lesions were visible.

[c] After CT scan with contrast substance and in thinner section, all lesions were visible.

[d] Denominator is the number of cysts diagnosed by contrast-enhanced MRI; sensitivity of MRI=100% (102/102), and sensitivity of contrast-enhanced CT scan=84.3% (86/102).

Parenchymal calcified lesions

In a case series, Suss et al. *(20)* found that CT scans showed calcification in five of eight patients, while MRI showed calcification in only one. In a prospective descriptive study in children, Aguilar Rebolledo et al. *(6)* demonstrated that CT scan performed better than MRI in visualization of calcified lesions, with an agreement of 20% (Kappa 0.22). This study is not included in Table A4.1.4 because numbers could not be extrapolated from the published data. In a comparative study of 50 patients by Zee et al. *(25)*, CT scan showed calcification in 12 patients and MRI in only six. In a retrospective case series involving 56 patients with radiologically, pathologically or autopsy-confirmed neurocysticercosis, Martinez et al. *(14)* found that calcifications were better observed on CT scan (13 positive cases, 23%) than in MRI (8 positive cases, 14%). Teitelbaum et al. *(21)* found in a case series of 26 patients that CT scan revealed seven patients with calcification and MRI only three. Del Brutto et al. *(9)* found in a case series of 54 patients, of whom eight had undergone both MRI and CT scan, that calcifications were identified in two patients on CT scan for whom the MRI was negative. In a prospective case series, Roy et al. *(18)* found that MRI phase imaging (with multi-echo SWAN imaging) correlated with CT scan in calcification detection, and that MRI could also be used to characterize calcified neurocysticercosis lesions. Both techniques detected 52 calcified

lesions in 35 patients. In a case series, Del Brutto et al. *(10)* found that, in 258 elderly patients who underwent both CT scan and MRI, calcified neurocysticercosis was diagnosed in 28 with CT scan and in 18 with MRI. T2 and gradient echo were the most useful sequences. Susceptibility weighted sequences were not developed or used in most of these studies.

Table A4.1.4. Frequencies of detection of cases and negative controls by MRI and CT scan in patients with calcified neurocysticercosis

Reference	Frequency of detection (cases)		Frequency of detection (negatives)	
	MRI	CT scan	MRI	CT scan
20	20% (1/5)	100% (5/5)	100% (3/3)	100% (3/3)
22	50% (6/12)	100% (12/12)	–	–
21	42.9% (3/7)	100% (7/7)	100% (3/3)	100% (3/3)
9	0% (0/2)	100% (2/2)	100% (6/6)	100% (6/6)
14	61.5% (5/13)	100% (13/13)	100% (43/43)	100% (43/43)
18[a]	100% (52/52)	100% (52/52)	–	–
10	64.3% (18/28)	100% (28/28)	100% (220/220)	100% (220/220)

Patients with calcified neurocysticercosis were defined as those with positive MRI or CT scan for parenchymal calcifications. Patients without calcified neurocysticercosis were defined as those with negative MRI and CT scan for parenchymal calcifications.

[a] These authors reported the number of lesions and used the MRI multi-echo SAWN protocol.

Subarachnoidal neurocysticercosis

No studies were found in which quantitative findings of subarachnoidal neurocysticercosis by MRI and CT scan were compared. Most of the case reports are descriptive and favour MRI over CT scan *(6)*.

Ventricular neurocysticercosis

Barloon et al. *(7)* presented a case series of 21 patients with lesions involving the fourth ventricle. In three patients who had received both MRI and CT scans, the diagnosis of cysticercosis was confirmed by surgery and pathology, while only one was identified as neurocysticercosis on MRI. Teitelbaum et al. *(21)* found in a case series that MRI identified an intraventricular cyst in six of seven cases of ventriculomegaly, while CT scan identified no lesions. In a retrospective study, Martinez et al. *(14)* found that 11 cases of intraventricular neurocysticercosis diagnosed by MRI were not detected by CT scan. Govindappa et al. *(13)* presented a case series of 11 patients who showed only obstructive hydrocephalus on CT scan, whereas ventricular neurocysticercosis was identified with MRI. In a retrospective study, Citow et al. *(8)* found that MRI performed significantly better than CT for ventricular neurocysticercosis; of 30 cases diagnosed by MRI, only three were identified by CT scan. The authors concluded that CT scan is suboptimal for diagnosing intraventricular neurocysticercosis because cysts often have similar density to cerebrospinal fluid, and the shape is not pathognomonic *(8)*. Gongora-Rivera et al. *(12)* conducted a clinical trial of patients with subarachnoid and ventricular neurocysticercosis. Of the 14 cases of ventricular neurocysticercosis diagnosed by MRI, only two were identified with CT scan. False positives were excluded because of alternative diagnoses at MRI (chronic arachnoiditis that caused entrapment of the fourth ventricle and a neoplasm).

Table A4.1.5. Frequencies of detection of cases and negative controls by MRI and CT scan in patients with ventricular neurocysticercosis

Reference	Frequency of detection (cases)		Frequency of detection (negatives)	
	MRI	CT scan	MRI	CT scan
7	33.3% (1/3)	0% (0/3)	–	–
21	85.7% (6/7)	0% (0/7)	–	–
14	100% (11/11)	0% (0/11)	–	–
13	100% (11/11)	0% (0/11)	–	–
8	100% (30/30)	10% (3/30)	–	–
12[a]	100% (12/12)	100% (12/12)	100% (2/2)	0% (0/2)

Patients with ventricular neurocysticercosis were defined as those with positive MRI and/or pathological confirmation. Patients without ventricular neurocysticercosis were defined as those with negative ventricular cysts at MRI or pathological confirmation of alternative diagnoses.

[a] Cases were diagnosed by CT imaging as highly suggestive of neurocysticercosis.

Spinal neurocysticercosis

No studies were found on spinal neurocysticercosis diagnosed by MRI as compared with CT scan. Most experts recommend MRI for evaluation of this neurocysticercosis presentation *(6)*.

Table A4.1.6. Summary of findings on the frequencies of detection of cases and negative controls by MRI and CT scan for different forms of neurocysticercosis

Form of neurocysticercosis	MRI	CT scan
Parenchymal viable	+++	++
Parenchymal granuloma	+++	+
Parenchymal calcified	+	+++
Ventricular	+++	+
Subarachnoid	+++	+
Spinal	+++	+

Contrast enhancement improved case detection with both CT scan and MRI.

+++ = good, ++ fair, + poor. Agreed by the expert panel because none of the studies included this comparison.

Quality assessment

GRADE criteria cannot be applied to this question.

The quality appraisals are shown in figures A4.1.1 and A4.1.2. Evaluation with the QUADAS-2 tool showed high risks of bias for patient selection, flow and timing (four studies) in the studies. This is not a significant concern regarding applicability. In general, the studies of the index test (CT scan) did not have higher risks of bias or raise concern about applicability.

Fig. A4.1.1. Risk of bias and concern about applicability in studies with CT scan as the index test and MRI as the comparator or reference test. The reference standard is both CT scan and MRI (gold standard).

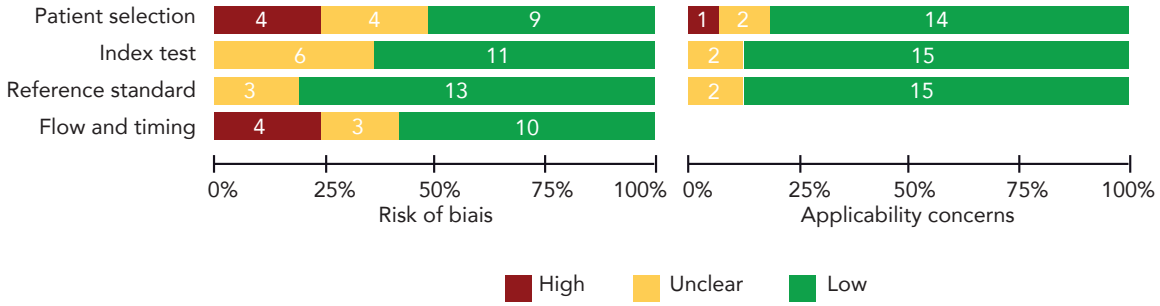
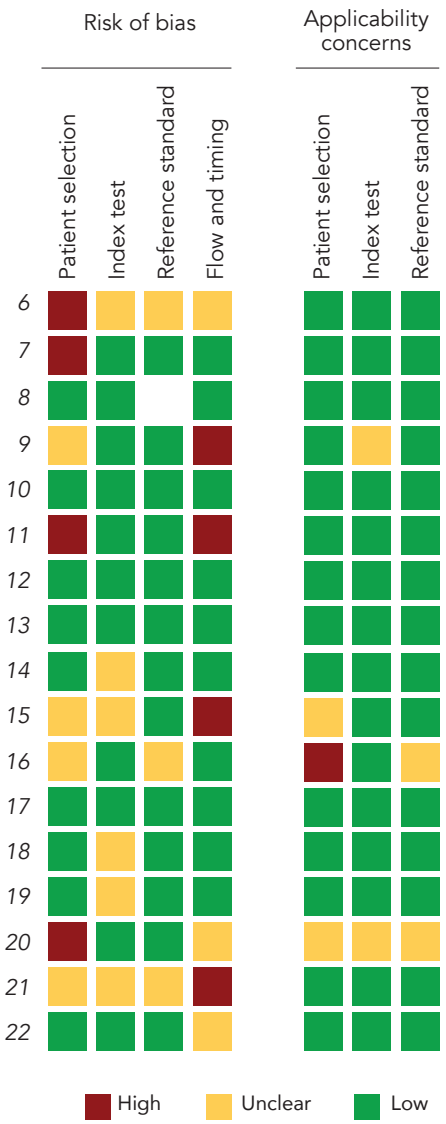


Fig. A4.1.2. Risk of bias and concern about applicability of studies with CT scan as the index test and MRI as the reference or comparator test



Evidence for recommendations

1	For people with neurocysticercosis, is use of MRI as the first-line imaging technique more accurate than a CT scan?
Factor	Explanation
Narrative summary of the evidence base	Six studies showed that the frequency of detection of cases on MRI is good while that on CT scan is fair for parenchymal viable neurocysticercosis. Five studies showed that the frequency of detection of cases on MRI is good while that on CT scan is poor for parenchymal granuloma neurocysticercosis. Eight studies showed that the frequency of detection of cases on MRI is poor while that on CT scan is good for parenchymal calcified neurocysticercosis. Six studies showed that the frequency of detection of cases on MRI is good while that CT scan is poor for ventricular neurocysticercosis.
Summary of the quality of evidence	Quality appraisal was conducted. GRADE criteria are not applicable.
Values and preferences, including any variation and human rights issues	The clinical evidence for use of MRI or CT scan to diagnose neurocysticercosis is strong. MRI is more sensitive than CT scan for detecting most neurocysticercosis types and can be used to detect other neurological conditions. MRI is less sensitive than CT scan for detecting small calcified lesions.
Costs and resource use and any other relevant feasibility issues	MRI is more expensive and less accessible than CT scan. MRI and CT scan require doctors trained in interpretation. MRI and CT scan require maintenance, which is expensive and often unavailable, and both require a stable electrical power supply.
FINAL RECOMMENDATION(S) MRI is the tool of choice in the diagnosis of neurocysticercosis, particularly when parenchymal viable, parenchymal granuloma or neurocysticercosis of the cerebellum, brain stem, ventricular, subarachnoid and spinal spaces is suspected. The benefits outweigh the risk of harm because of possible inappropriate patient management, morbidity and mortality if subarachnoi or intraventricular neurocysticercosis is not diagnosed with appropriate imaging. CT is the tool of choice for detecting small calcified lesions. REMARKS: CT scan should be used as an alternative when MRI is unavailable or contraindicated.	
CLINICAL AND REGIONAL CONSIDERATION(S) The benefit of the test should outweigh the risk of harm, including the risk of exposure to radiation from CT and allergic reactions or renal failure from use of contrast media. Access to neuroimaging in LMICs.	

RESEARCH GAP(S)

How accessible are neuroimaging facilities for neurocysticercosis diagnosis in LMICs?

How can access to neuroimaging facilities for diagnosis of neurocysticercosis and other neurological diseases be increased?

STRENGTH OF THE RECOMMENDATION(S)

Strong because of the potential for inappropriate patient management, morbidity and mortality if subarachnoid or intraventricular neurocysticercosis is not diagnosed and because neurocysticercosis-induced epilepsy is treatable if identified.

ADDITIONAL REMARKS:

Contrast-enhancing agents improve the diagnostic accuracy of both MRI and CT scan but are not required for detection of calcifications. Furthermore, contrast adds expense and carries risks of additional toxicity.

The type of CT scan and MRI as well as the skill of the radiologist might influence performance. Many of the studies reviewed date from the 1980s and 1990s, and machine performance has since evolved.

EVIDENCE PROFILE: QUESTIONS 2 AND 3

2	In individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
Population	Individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts
Intervention	Anthelmintic therapy (ALB, PZQ) and symptomatic treatment (anti-inflammatory and AEDs)
Comparator	Symptomatic treatment alone (anti-inflammatory and/or AEDs)
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

3	In individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts, is anti-inflammatory therapy associated with better clinical outcomes than either anthelmintic or AED treatment alone?
Population	Individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts
Intervention	Anti-inflammatory therapy and anthelmintic or AED treatment alone
Comparator	Either anthelmintic or AED treatment alone
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

Background

T. solium has a complex two-host life cycle. Humans are the only definitive host and harbour the adult tapeworm, whereas pigs act as the intermediate host and harbour the larvae (known as cysticerci). Humans may also become infected by accidental ingestion of *T. solium* eggs through faecal–oral infection. The embryos contained in the eggs cross the intestinal mucosa, are transported by the circulatory system and are distributed throughout the body. Once they reach a small terminal vessel, the embryos enlarge and encyst to form larval vesicles or cysticerci, reaching their definitive size within 2–3 months. Symptoms usually result from parasites located in the nervous system *(27)*.

Neurocysticercosis is pleomorphic because of individual differences in the number, topography and evolutionary stage of lesions and the severity of the host's immune response to the parasites. Symptoms typically develop years after initial infection. Symptoms may be due to an inflammatory response to at least one of the brain parasites or to hydrocephalus caused by mechanical obstruction of the ventricles or obstruction of cerebrospinal fluid outflow from subarachnoid cysts. A large proportion of symptomatic patients with cysts in the brain parenchyma (intraparenchymal neurocysticercosis) present with seizures and have a good prognosis *(28, 29)*. After an undetermined length of time, cysts become inflamed, and degeneration begins. Initially, there is evidence of inflammation, with enhancement of the cyst wall or surrounding oedema. Later, the vesicular fluid becomes opaque and dense, and the cyst's edges become irregular and shrink. Degenerating parasites are surrounded by a thick collagen capsule, and the brain parenchyma shows astrocytic gliosis associated with microglial proliferation, diffuse oedema, neuronal degenerative changes and perivascular cuffing of lymphocytes. Radiologically, lesions in this stage appear as single nodular or annular lesions, which are clearer after administration of contrast medium. Later, in some lesions, calcification starts, usually in the cephalic portion of the parasite, and progresses to the vesicular wall *(30)*.

When specific anthelmintic agents (initially PZQ and later ALB) were introduced, some authors hypothesized that there was no need to hasten the natural inflammation that accompanies the death of the parasite caused by these agents *(31–33)*. This led to debate in the literature about whether anthelmintic treatment or natural involution of a cyst results in less scarring and thus a better prognosis in terms of the evolution of epilepsy. Currently, there is a consensus that use of anthelmintic drugs is of some benefit in cases with viable parasites, despite their inconsistent antiparasitic efficacy. During the initial days of treatment, neurological symptoms frequently increase because of exacerbated inflammation around the dying larvae. The symptoms are usually limited to seizures. Other symptoms, such as headaches, focal neurological signs, dizziness and vomiting, are often reported in the days after anthelmintic treatment; however, there is limited reporting of symptoms other than seizures.

This systematic review was conducted to evaluate the literature on the benefits and harms of using anthelmintic drugs (ALB or PZQ) in individuals with viable parenchymal neurocysticercosis who are taking AEDs as compared with those not using such drugs with respect to reduction in the frequency of symptoms after treatment (seizures) (question 2). The group also evaluated use of anti-inflammatory drugs and AEDs with or without anthelmintic treatment as compared with AEDs with or without anthelmintic treatment. The outcomes evaluated were better clinical outcome, faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status (question 3).

Inclusion and exclusion criteria

The search strategy and results are given in Annex 3 and section 2.3.2 (Fig. 3), respectively.

INCLUSION CRITERIA	
Types of studies:	Experimental and observational studies (questions 2 and 3)
Types of participants:	Symptomatic individuals with at least one well defined intraparenchymal viable *T. solium* cyst (questions 2 and 3)
Types of intervention:	The intervention group received ALB or PZQ in combination with AEDs and anti-inflammatory drugs. The controls may have received AEDs only or in combination with anti-inflammatory drugs, but no anthelmintic treatment (question 2). The intervention group may have received anti-inflammatory therapy combined with AEDs with or without anthelmintic drugs. Controls received AED treatment with or without anthelmintic but no anti-inflammatory treatment (question 3).
Types of outcome measures:	At least one of either (i) cyst resolution; (ii) incidence rate of seizures (question 4); and (iii) resolution of neurological symptoms/ signs (question 3).
Exclusion criteria:	Case series and case reports were excluded (questions 2 and 3). Neurocysticercosis patients with lesions other than intraparenchymal cysticercosis, such as subarachnoid, ventricular, ocular or spinal cysticercosis, were excluded (Patients with concomitant calcification or enhancing lesions will be considered.) (question 2). Neurocysticercosis patients other than with viable neurocysticercosis lesions were excluded (question 3).

Summary of findings

Question 2

A total of eight RCTs were identified for use in answering question 2. The main characteristics are described below and summarized in Table A4.2.1. According to the quality assessment (see section A4.2.5, figures A4.2.1 and A4.2.2), only four studies were suitable for detailed presentation *(34–37)*. Of these, that by Alarcon et al. *(34)* was excluded because the authors did not use corticosteroids during anthelmintic treatment, consistent with current standards of care. That by Das et al. *(36)* was also excluded, because of inconsistences in the outcomes (seizures and cyst resolution) and adverse events. The study by Romo et al. *(33)* was included, however, as it is a re-analysis of the study of Carpio et al. *(35)*.

Table A4.2.1 Summary of studies included and main findings for question 2

Study	Study design	Total no. of patients (M, F)	Mean age (years)	Mean no. of cysts (range)	Follow-up for CE and SZ	Intervention (cysticidal drug)	Intervention (corticosteroids)	Patients with no active lesion n/n (%)[a]	Patients free of seizures n/n(%)	Study quality[b]
38	Non-blinded RCT	23; M: 11, F: 7	31	1.6 (1–3)	CE: CT scan after 3 months SZ: NA	Group A: 3 days of ALB, 15 mg/kg per day	No corticosteroids	5/9 (56)	NA	Poor NA
						Group B: 4 weeks of ALB, 15 mg/kg per day	No corticosteroids	6/9 (67)	NA	
						Group C: No therapy	No corticosteroids	0/5 (0)	NA	
34	Non-blinded RCT	89; M: 36, F: 47	33.4	1.8 (1–6)	CE: CT scan after 3 and 12 months SZ: 31.4 months	Group A: 3 days of ALB, 15 mg/kg per day	No corticosteroids	13/27 (48)	8/18	Fair Fair
						Group B: 1 week of ALB, 15 mg/kg per day	No corticosteroids	15/27 (56)	10/20	
						Group C: No therapy	No corticosteroids	2/29 (7)	9/20	
39	Non-blinded RCT	175; M: 73, F: 65	40	5.1 (1–NR)	CE: CT scan after 3–6 months and 9–12 months SZ: 24 months	Group A: 1 week of ALB, 15 mg/kg per day	2 weeks of PRED, 1 mg/kg per day	16/57 (28)	33/52 (63)	Poor Poor
						Group B: 2 weeks of PZQ, 50 mg/kg per day	2 weeks of PRED, 1 mg/kg per day	17/54 (31)	26/45 (58)	
						Group C: No therapy	2 weeks of PRED, 1 mg/kg per day	5/27 (19)	12/21 (57)	

35	Double-blind RCT	178; M: 97, F: 77	40.5	Parenchymal: NR Extraparenchymal	CE: CT or MRI after 1, 6 and 12 months SZ: 24 months	Group A: 8 days of ALB 15 mg/kg per day (max, 800 mg/day) Group B: Placebo, 8 days	PRED for 1 week, 8 days and 8 days at 1.5, 1 and 0.5 mg/kg per day PRED for 1 week, 8 days and 8 days at 1.5, 1 and 0.5 mg/kg per day	20/39 (51) 8/27 (30)	25/52 (48) 24/55 (44)	Fair Fair
36	Double-blind RCT	300; M: 178, F: 122	29	NR ± 3.7 (2–7)	CE: CT scan after 3 months and every 6 months until resolution for 5 years SZ: 5 years	Group A: 2 weeks of ALB at 15 mg/kg per day Group B: 2 weeks of placebo	2 weeks of DXM at 6 mg/day No corticosteroids	10/148 (7) 12/150 (8)	NC NC	Fair Fair
37	Double-blind RCT	120; M: 61, F: 59	33	NR 5 (1–20)	CE: MRI after 6 months and CT scan after 12 and 24 months SZ: 30 months	Group A: 10 days of ALB at 800 mg/day Group B: placebo	10 days of DXM at 6 mg/day No corticosteroids	21/55 (38) 8/54 (15)	32/57 (56) 30/59 (51)	Good Good
40	Double-blind RCT	29; M: 22, F: 7	25	5.1 (NR)	CE: CT scan after 1 and 3 months SZ: NA	Group A: 1 week of ALB at 15 mg/kg per day Group B: 1 week of placebo	No corticosteroids No corticosteroids	14/16 (87) 10/13 (77)	NA NA	Poor NA
41	Non-blinded RCT	25; M: 17, F: 8	39.5	5.3 (1–12)	CE: CT scan after 3 months SZ: NA	Group A: 4 weeks of ALB at 15 mg/kg per day Group B: 2 weeks of PZQ at 50 mg/kg per day Group C: No therapy	No corticosteroids No corticosteroids Corticosteroids	6/10 (60) 7/10 (70) 0/5 (0)	NA NA NA	Poor NA

ALB: albendazole; CE: cyst evolution; CT: computerized tomography; NA: not applicable; NR: not reported; NC: not comparable; PRED: prednisolone; RCT: randomized controlled trial; PZQ: praziquantel; SZ: seizures

[a] Proportion of patients with no viable cysts reported after brain imaging 3–6 months after intervention; includes patients with parenchymal and extraparenchymal cysts at baseline.

[b] Study quality was rated according the two main outcomes: cysticidal effect and effect on seizures.

This outcome was analysed separately by Garcia et al. *(37)* and Carpio et al. 2008 *(35)*; however, the results are not comparable because the duration of ALB therapy was different (10 versus 8 days) and the corticosteroid used was different (DXM plus anthelmintic drugs in the intervention group by Garcia et al. and prednisolone (PRED) for both the intervention and the control group by Carpio et al.). Hence, the study by Carpio et al. *(35)* is the only one in which the effect of the anthelmintic drug was distinguished.

Seizure control

Other differences between the studies include the pleomorphic presentation of parenchymal viable cysts, with differences in mean and range of numbers, location, size and perilesional oedema and potential calcification as the outcome after anthelmintic treatment. Additionally, seizures after anthelmintic treatment were evaluated differently, such as the length of follow-up, classification of epilepsy and analysis and presentation of the results. The results of each study are thus presented separately.

Of the 178 randomized participants included by Carpio et al. *(35)*, only 107 reported new-onset seizures at enrolment. Some participants presented with a history of seizures and viable or degenerate parenchymal cysts, while others also had extra-parenchymal neurocysticercosis, so that it was difficult to interpret whether anthelmintic treatment reduced seizures. After 1 year, Carpio et al. *(35)* reported that the proportion of patients free of seizures was not significantly different with ALB (62%) and in the control group (52%). No difference was found between patients with intraparenchymal cysts (viable and degenerating lesions) and those with extra-parenchymal cysts (with or without parenchymal cysts). A secondary analysis of this cohort of patients was reported by Romo et al. *(33)*, who presented the results after 2 years of follow-up.

Reduction in number of seizures: ALB resulted in a statistically significant reduction in generalized seizures between 1 and 12 months (unadjusted relative risk [RR], 0.19 ; 95% confidence interval [CI], 0.04 ; 0.91; ALB n=55 vs placebo n=59) and between 1 and 24 months (unadjusted RR, 0.06; 95% CI, 0.01 ; 0.57; ALB n=35 vs placebo n=37) in patients with seizures and neurocysticercosis at baseline. The reduction was also significant when the analysis was restricted to patients with active lesions only during months 1–12 (RR, 0.07; 95% CI, 0.01 ; 0.78; ALB n=36 vs placebo n=28). ALB had no statistically significant effect on reducing the number of focal or generalized seizures regardless of time.

People free of epilepsy: There was no significant difference in the number of people free of epilepsy during the 2 years of follow-up between the ALB group (25/52, 48%) and the placebo group (24/55, 44%).

In the study of Garcia et al. *(37)*, all the patients had epilepsy, with < 10 years of seizures at enrolment.

Reduction in number of seizures: During follow-up (2–30 months after anthelmintic and corticosteroid treatment), a 46% reduction in the number of seizures was reported from that in the placebo group (95% CI, 74% ; 83%); however, the difference was not statistically significant. When the results were analysed by seizure type, the reduction in the number of partial seizures (41%, 95% CI, –124% ; 84%) was not significant; however, the reduction in the number of generalized seizures was significant (67%, 95% CI, 20% ; 86%). The authors concluded that the difference in the number of partial seizures was due to the small number of patients with many seizures. Thus, the proportions of patients with partial seizures during follow-up were similar in the two groups (19/57 with ALB and 16/59 with placebo). Patients in the placebo group were more likely to present with generalized seizures (22/59) than those the ALB group (13/57) (RR, 1.63 ; 95% CI, 0.91 ; 2.92).

People free of epilepsy: There was no difference in the number of people free of epilepsy during follow-up in the ALB group (32/57, 56%) and in the placebo group (30/59, 51%).

Cysticidal effect: Reporting of radiological outcomes varied. Garcia et al. *(37)* used MRI to measure outcomes, while Carpio et al. *(35)* did not clearly distinguish CT scan and MRI results. The interval

between treatment and imaging differed in the two studies, obviating comparison of outcomes. Despite these differences, both studies showed that anthelmintic treatment had a greater cysticidal effect than no treatment or placebo.

In the study by Carpio et al. *(35)*, 178 participants with neurocysticercosis were randomized to receive ALB plus corticosteroids or a placebo with corticosteroids. Of these, only 84 (47%) participants had an active parenchymal cyst at baseline (45 in the ALB group and 39 in the placebo group). Neuroimaging (CT scan or MRI) was performed 1, 3 and 12 months after treatment.

Reduction in the number of cysts: No data.

Number of patients with parenchymal neurocysticercosis free of viable cysts: The proportion of patients in whom cysts disappeared after anthelmintic treatment was statistically significantly higher in the ALB group than in the placebo group at months 1 (40.9% [18/44] vs 10.8% [4/37] $P = 0.002$), 6 (48.7% [19/9] vs 22.9% [8/27] $P = 0.021$) and 12 (48.8% [20/41] vs 19.4% [7/36] "$P = 0.007$").

Garcia et al. *(37)* initially included 120 participants, with follow-up evaluation by MRI at 6 months performed in 109 patients (55 in the ALB group and 54 in the placebo group).

Reduction in the number of cysts: Analyses were performed separately for people with uninflamed cysts and cysts with early signs of inflammation. ALB has greater cysticidal efficacy in people with uninflamed cysts, with 41% (79/192] of cysts persisting unchanged as compared with 87% (243/279] in the placebo group ("$P < 0.001$"; RR for persistence of cysts with placebo, 2.12; 95% CI, 1.59 ; 2.81). A similar trend was found for cysts that showed early signs of inflammation, the proportion of cysts persisting after treatment also being lower in the ALB group (21%, 10/48) than in the placebo group (49%, 29/59) ("$P = 0.013$").

Number of patients free of viable cysts: Six months after anthelmintic treatment, no active lesions were found in 38% (21/55) of patients in the ALB group and in 14.8% (8/54] of patients in the placebo group ("$P = 0.007$").

Adverse events

Carpio et al. *(35)* summarized possible adverse events as shown in Table A.4.2.2.

Table A4.2.2. Numbers of patients with possible adverse events of treatment

Symptom	ALB	Placebo	No. (% valid responses) with symptom
During 8 days of treatment			
Seizures	2 (2.4)	3 (3.5)	1.00[a]
Headache	59 (70.2)	53 (61.6)	0.236
Stomach problems (nausea, pain, or vomiting)	38 (45.2)	40 (46.5)	0.868
Intracranial hypertension	0	3 (0.5)	0.246[a]

Table A4.2.2. Continued

Symptom	ALB	Placebo	No. (% valid responses) with symptom
During first month after treatment			
Seizures	8 (9.8)	10 (12.0)	0.637
Headache	50 (61.0)	51 (61.4)	0.951
Stomach problems (nausea, pain, or vomiting)	9 (11.0)	13 (15.7)	0.376
Intracranial hypertension	0	0	

[a] Fisher's exact test.

The most commonly reported problems were headache, seizures and stomach problems. Of the seven people who died during the study period (two in the treatment group and five in the placebo group), however, most had extra-parenchymal neurocysticercosis.

Garcia et al. *(37)* observed the same proportions of side-effects during treatment in both study groups; however, abdominal pain was reported more often in the treatment group (Table A4.2.3).

Table A4.2.3. Side-effects in the groups given albendazole and placebo in the study of Garcia et al. *(37)*

Side-effect	No. of patients		P
	Albendazole (n=7)	Placebo (n=59)	
Neurological			
Partial seizures	8	5	0.51
Seizures with generalization	2	1	0.62
Headache	32	31	0.84
Paresthesia	1	3	0.62
Paresis	1	0	0.49
Dizziness	9	4	0.21
Non-neurological			
Abdominal pain	8	0	0.006
Diarrhoea	2	0	0.24
Rash	0	1[a]	1.00
Other	2	1	0.62

[a] Rash remitted immediately after suspension of phenytoin.

Question 3

The search did not identify any RCTs in which anti-inflammatory treatment alone was compared with anthelmintics and/or AEDs for neurocysticercosis with viable parenchymal lesions. Corticosteroids were used in the comparison group in four RCTs, but in conjunction with AED.

Cuello-Garcia et al. *(42)* reported the results of a meta-analysis of 13 RCTs of use of corticosteroids in neurocysticercosis; however, only four studies (the same studies found in our search) involved parenchymal viable cysts *(35–37, 39)*. The other nine studies were RCTs of patients with a SEL. Garcia et al. *(43)* also reported the results of an evaluation of the role of corticosteroids in the treatment of intraparenchymal viable cysts. The main findings of the selected additional papers are summarized in Table A4.2.4.

Table A4.2.4. Main findings of selected additional papers for question 3

Reference	No. of patients (total and by gender)	Intervention		
		Cysticidal drug	Corticosteroids	AEDs
39	175; M: 73, F: 65	Group A: 1 week of ALB at 15 mg/kg per day Group B: 2 weeks of PZQ at 50 mg/kg per day Group C: No therapy	2 weeks of PRED at 1 mg/kg per day 2 weeks of PRED at 1 mg/kg per day 2 weeks of PRED at 1 mg/kg per day	Carbamazepine or phenytoin when required Carbamazepine or phenytoin when required Carbamazepine or phenytoin when required
35	178; M: 97, F: 77	Group A: 8 days of ALB at 15 mg/kg per day (maximum, 800 mg/day) Group B: Placebo	1 week, 8 days and 8 days of PRED at 1.5, 1 and 0.5 mg/kg per day 1 week, 8 days and 8 days of PRED at 1.5, 1, and 0.5 mg/kg per day	Carbamazepine or phenytoin when required Carbamazepine or phenytoin when required
36	300; M: 178, F: 122	Group A: 2 weeks of ALB at 15 mg/kg per day Group B: Placebo	2 weeks of DXM at 6 mg/day No corticosteroids	Phenytoin n=80 Carbamazepine n=60 Valproate n=10 Phenytoin n=76 Carbamazepine n=68 Valproate n=6
37	120; M: 61, F: 59	Group A: 10 days of ALB at 800 mg per day Group B: Placebo	10 days of DXM, at 6 mg/day Placebo	AED AED

43	64; M: 21, F: 43	Both groups: 14 days of ALB at 800 mg/day	Group A: DXM at 6 mg/day for 10 days	AED
			Group B: DXM at 8 mg/day for 28 days and then decreasing doses every 2 days to 6, 4, 3, 2, 1 mg and 0.5 mg for 4 days	AED

Treatment with corticosteroids was not compared with cysticidal drugs or AED treatment alone in any of the studies included. The effect of corticosteroids on seizure reduction could not be evaluated. In the studies of Das et al. *(36)* and Garcia et al. *(43)* in which anthelmintic treatment and corticosteroids were compared with placebo, the effect of corticosteroids cannot be distinguished from that of anthelmintic therapy. Additionally, the study of Das et al. *(36)* showed serious data inconsistencies, including in *P* values, confidence intervals and denominators. Carpio et al. *(35, 39)* compared corticosteroids and anthelmintic therapy with corticosteroids alone, so that the observed effect could be attributed to the anthelmintic drug, summarized under question 2. In all four studies, a first-line AED (such as carbamazepine or phenytoin) was given to all participants.

Garcia et al. *(43)* evaluated the role of corticosteroids in the treatment of intraparenchymal viable cysts, at two doses and durations of corticosteroid treatment in combination with anthelmintic treatment. In this open-label RCT, DXM at 6 mg/day (n=32) for 10 days (conventional scheme) was compared with DXM at 8 mg/day (n=32) for 28 days. Each treatment was followed by a 2-week tapering-off period (enhanced scheme) in patients with viable neurocysticercosis (with fewer than 20 cysts) receiving ALB.

The study outcomes included the number of days with seizures and the number of patients with seizures, both measured between 11 and 42 days after the end of treatment. In additional analyses, results on days 1–10, 11–21, 22–32, 33–42, 43–60 and 61–180 were compared. In the main analysis (days 11–42), fewer seizures were observed with the enhanced scheme, but the difference was not statistically significant (12 vs 49 patient-days with seizure, ("*P* = 0.114"). The numbers of patients with seizures in this period were also non-significantly different; however, during the first 10 days, when patients were treated with ALB, there were significantly fewer patient-days with seizures and individuals with seizures in the group receiving enhanced steroids than in that receiving conventional doses (days 1–10 after anthelmintic treatment: 4 vs 17 patient-days with seizures ("*P* = 0.004") and 1 vs 10 patients with seizures ("P = 0.003") and after DXM cessation (days 11–21 after anthelmintic treatment: 6 vs 27 patient-days with seizures ("P = 0.014"); and 4 vs 12 patient-days with seizures ("P = 0.021") but not after day 21. In both the conventional and the enhanced scheme, differences in anthelmintic efficacy or the occurrence of relevant adverse events were not significant. Thus, in patients with viable intraparenchymal neurocysticercosis, higher doses of DXM (8 mg vs 6 mg) and longer treatment (28 days with 2 weeks of tapering off versus 10 days) can reduce the incidence rate of seizures and the cumulative incidence of seizures during the first 21 days after anthelmintic treatment. The effectiveness of the higher corticosteroid scheme, however, decreases with time after treatment.

Another important consideration is use of corticosteroids alone in massive brain cysticercosis. Anthelmintic treatment can incur important risks due to inflammation caused by infections (for example, death, encephalitis, intracranial hypertension). Therefore, in patients with this type of neurocysticercosis, anti-inflammatory therapy without anthelmintic treatment is the recommended approach. This conclusion is based on expert opinion, and no clinical trials have been performed because of ethical considerations.

Quality assessment

The studies included in question 2 were found to be of moderate quality according to the GRADE criteria and therefore provide a good indication of the probable effect (Table A4.2.5). GRADE analysis was not performed for question 3 because there were too few studies.

Table A4.2.5. GRADE quality assessments of studies for question 2

No. of participants (No. of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other: Confounding	Quality of evidence
Outcome: Seizures: reduction in number of seizures; people free of seizure						
227 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	Serious	⊕⊕◎ Moderate
Outcome: Cysticidal effect: reduction in number of cysts; patients free of viable cysts						
201 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	Serious	⊕⊕◎ Moderate

The quality appraisal is shown in figures A4.3.1 and A4.3.2. The summary of the risk of bias indicated that four studies were suitable for detailed presentation for question 2 *(34–37)*. The study by Alarcon et al. *(34)* was, however, excluded because the authors did not administer corticosteroids during anthelmintic treatment, and that approach is no longer advisable according to current standards of care. The RCT reported by Das et al. *(36)* was excluded because of several inconsistencies in outcomes (seizures and cyst resolution) and adverse events. Quality assessment was not performed for question 3 because of the lack of RCTs on this question.

Fig. A4.2.1. Risks of bias in studies for question 2

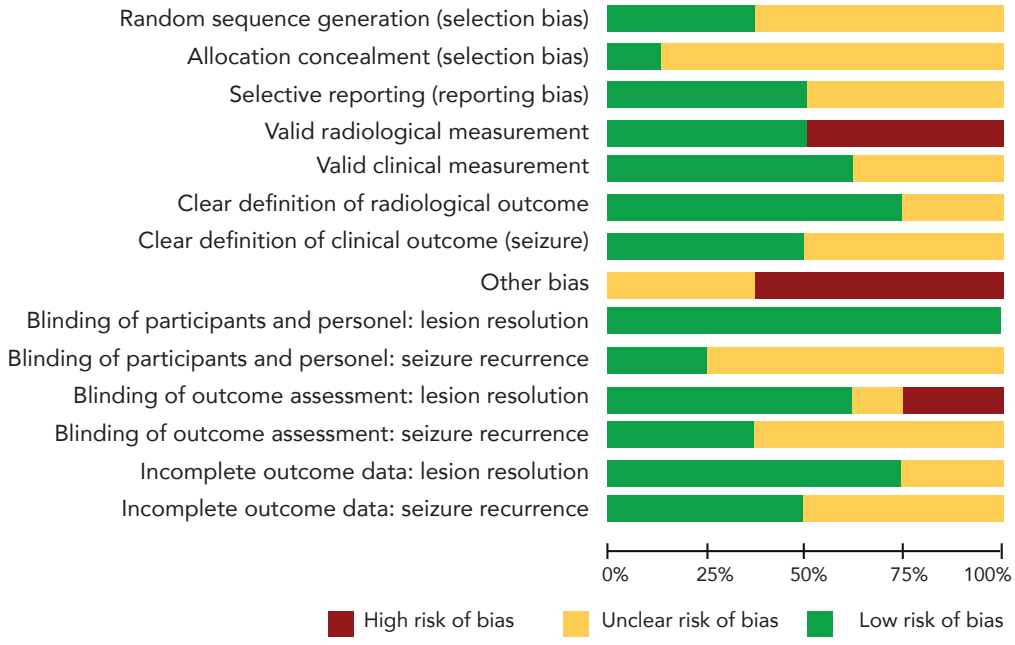
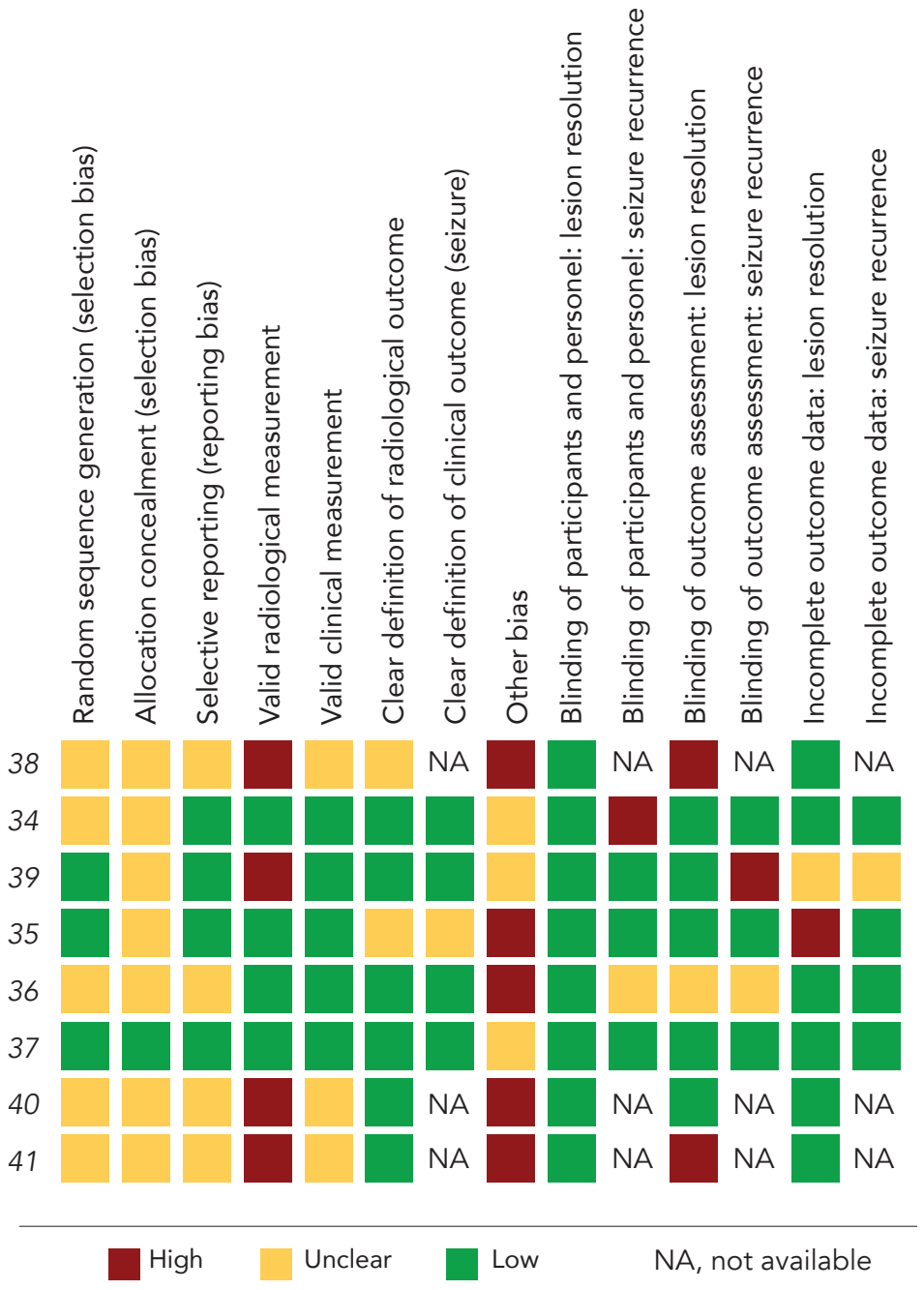


Fig. A4.2.2. Summary of risks of bias in studies for question 2



Evidence to recommendations

2	In individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
3	In individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts, is anti-inflammatory therapy associated with better clinical outcomes than either anthelmintic or AED treatment alone?
Factor	Explanation
Narrative summary of evidence base	The information below refers mainly to PICO 2, as there were no suitable RCTs for PICO 3. Eight RCTs were found for PICO 2. Because of the high risk of bias in six studies, only two studies were included; further, because several factors could not be compared, the evidence from the different studies could not be synthesized. Seizure control: As Romo et al. *(33)* re-analysed data from the study of Carpio et al. *(35)*, it was not counted as a separate study. When the analysis was restricted to patients with active parenchymal lesions *(33)* during months 1–12, the reduction in the number of generalized seizures was significant (ALB n=36 vs placebo n=28; RR, 0.07; 95% CI, 0.01 ; 0.78). Garcia et al. *(37)* found no difference in the numbers of people free of seizures among the groups. The reduction in the number of partial seizures was not significant, but more people in the ALB group had a reduction in the number of generalized seizures. Patients receiving placebo were more likely to present seizures with generalization (22/59 versus 13/57 in ALB group; RR, 1.63; 95% CI, 0.91 ; 2.92). Cysticidal effect: Carpio et al. *(35)* showed a larger statistically significant effect in patients in whom cysts disappeared after anthelmintic treatment in the ALB group than with placebo. Information on the reduction in the number of cysts was not provided. Garcia et al. *(37)* found a significant difference in the reduction in the number of cysts in uninflamed cysts and in cysts with early signs of inflammation. The number of patients free of viable cysts was also higher in the ALB group. Adverse events: Carpio et al. *(35)* found no significant difference. Garcia et al. *(37)* found a significantly higher occurrence of abdominal pain only in the ALB group.

Summary of the quality of evidence	Because of risks of bias in the initial eight RCTs, only two were considered further. The quality of the evidence for comparing seizure frequency was moderate because of the presence of confounding factors. The quality of the evidence for comparing cysticidal effect was moderate because of serious inconsistency and other confounding factors.
Balance of benefit and harms	The benefit of treatment (anthelmintic treatment in combination with corticosteroids) of symptomatic people with active neurocysticercosis outweighs the harm.
Values and preferences including variation and human rights issues	The perspective of people with epilepsy or seizures indicates the following: factors in favour of anthelmintic treatment of symptomatic individuals with active neurocysticercosis: importance of the intervention for better seizure control, importance of the intervention for better cyst resolution and importance of the outcomes for better social functioning, decrease in stigmatization and discrimination; and factors against anthelmintic treatment of symptomatic individuals with active neurocysticercosis: importance of adverse events due to intervention, importance of economic loss due to hospitalization for interventions and importance of lack of availability of neuroimaging facilities
Costs and resource use and any other relevant feasibility issues	Availability and price of anthelmintic therapy (on WHO List of Essential Medicines) Access to and costs of neuroimaging, which is standard practice before initiation of anthelmintic medication with corticosteroids Training of clinical personnel

Final recommendation(s)

Anthelmintic therapy, in combination with corticosteroids, should be provided to individuals with symptomatic neurocysticercosis and viable parenchymal brain cysts for better outcomes in terms of cyst resolution and seizure control.

Clinical consideration(s) and regional consideration(s)

Although no systematic reviews were available, the clinical experience of experts indicates that anthelmintic drugs should not be used in patients with massive numbers of cysts and neurocysticercosis encephalitis. If inflammation is pronounced in these cases, patients should be treated with corticosteroids alone.

Research gaps

What is the optimal drug(s), dose and duration of combined anthelmintic therapy for individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

What is the effect of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) on seizure severity, frequency and long-term recurrence (> 2 years) and of reduced duration of AED therapy in individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

What is the impact of anthelmintic therapy on the formation of calcifications?

What are the adverse events of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) in individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

What is the optimal drug(s), dose and duration of anti-inflammatory therapy (corticosteroids) in individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

What is the effect of anti-inflammatory therapy (corticosteroids) alone on the severity, frequency and long-term recurrence of seizures and of reduced duration of AED therapy in individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

What are the adverse events of anti-inflammatory therapy (corticosteroids) alone in individuals with symptomatic neurocysticercosis with viable parenchymal brain cysts?

Strength of recommendation(s)

Strong

Additional remarks

No evidence was found for pregnant women or children. In those cases, expert advice should be sought.

EVIDENCE PROFILE: QUESTIONS 4 AND 5

4	In individuals with symptomatic neurocysticercosis with a SEL, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
Population	Individuals with symptomatic neurocysticercosis and a SEL
Intervention	Anthelmintic therapy (ALB) and symptomatic treatment (anti-inflammatory and/or AEDs)
Comparator	Symptomatic treatment alone (anti-inflammatory and/or AEDs)
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

5	In individuals with symptomatic neurocysticercosis with a SEL, is anti-inflammatory therapy associated with better clinical outcomes than AED treatment alone?
Population	Individuals with symptomatic neurocysticercosis and a SEL
Intervention	Anti-inflammatory therapy and AED treatment
Comparator	AED treatment alone
Outcome	Faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse, or more frequent achievement of seizure-free status

Background

A SEL is the most frequent presentation of neurocysticercosis on the Indian subcontinent *(17, 44, 45)*. SELs were recognized as early as 1980 on CT images of Indian patients with seizures but were considered to be granulomas due to tuberculosis. Histological study of these lesions subsequently showed that the vast majority were "cysticercal granulomas" *(46)*. Most resolve spontaneously without cysticidal drug therapy 12 years after presentation, leaving a calcified scar in approximately 20% of cases. Most patients with a SEL present with seizures or headaches. The seizures are usually well controlled with AEDs, although 20–30% of cases have at least one seizure relapse in the evolution of the condition *(47)*.

The systematic review was conducted to evaluate whether use of anthelmintic therapy in individuals with symptomatic neurocysticercosis with a SEL is associated with better clinical outcomes than symptomatic treatment alone (question 4) and whether use of anti-inflammatory therapy in these individuals is associated with better clinical outcomes than AED treatment alone (faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status) (question 5).

Inclusion and exclusion criteria

The search strategy and results are provided in Annex 3 and section 2.3.2 (Fig. 3), respectively.

INCLUSION CRITERIA for questions 4 and 5	
Types of studies:	Experimental and observational studies
Types of participants:	Individuals with a SEL with well-established diagnosis of epilepsy
Types of intervention:	The intervention group may have received any currently marketed anti-inflammatory therapy. The control group may have received any currently marketed AED.
Types of outcome measures:	Incidence rates of seizures and of neurological symptoms/signs
Exclusion criteria for questions 4 and 5:	Case series, case reports and studies of patients with neurocysticercosis but no SEL were excluded.

Summary of findings

The systematic search identified two relevant meta-analyses *(48, 49)*. Besides the studies included in those two meta-analyses *(34, 50–64)*, we identified three additional studies *(65–67)*.

Our group *(68)* conducted the analyses for PICO question 5 (corticosteroids), and the results of the quality assessment, meta-analysis and GRADE table are presented below. More detailed information can be found in the reference.

The 14 RCTs included by Zhao et al. *(48)* comprised a total of 1277 randomized patients, with a sex distribution of 29.7–47.2% for women and a mean age of 7.4–24 years at the beginning of the studies. All the studies were conducted in India. Further details are summarized in Table A4.3.1 and Fig. A4.3.1 (both from Zhao et al. *48*).

Table A4.3.1. Main characteristics of the RCTs included in the quantitative analysis

Ref.	Patients (N=1277)		Intervention[a]		Follow-up	Outcome		Risk of bias[b]
	N (M, F)	Age (years)	Anthelmintics	Corticosteroids		Seizure recurrence	Complete resolution	
50	75 (52, 23)	Mean, 21.8	ALB, 1 week Placebo	None None	CT scan after 1 and 3 months	NA NA	8/40 8/35	NA, moderate
52	73 (34, 29)	Mean, 7.4	ALB, 4 weeks Placebo	PRED 1–2 for 5 days	CT scan after 1 and 3 months, 15 months' total follow-up at 3-month intervals	7/31 11/32	20/31 12/32	Low, low

51	72 (38, 34)	1.5–12	ALB, 4 weeks Placebo	PRED 2 for 3 days PRED 2 for 3 days	CT scan after 6 months, 6 months' total follow-up	3/24 5/27	11/18 9/18	Low, low
53	123 (65, 58)	Mean, 7.6	ALB, 4 weeks None	DMX at 0.15 mg/kg per day for 5 days None	CT scan after 3 months, 6 months' total follow-up at 3-month intervals	6/45 15/45	14/45 9/45	High, high
54	97 (56, 41)	Mean, 22	None None	PRED 1 for 10 days, tapered off over next 4 days None	CT scans after 1 and 6 months, 6 months' total follow-up at 1-month intervals	1.49 6/48	43/49 25/48	High, high
56	110 (66, 44)	1–14	ALB, 4 weeks ALB, 4 weeks None	None PRED 2 for 1 week PRED 2 for 3 weeks, tapered off in week 4	CT scans after 3 and 6 months, 18 months' total follow-up at 3-month intervals	5/37 4/35 14/38	28/37 26/35 29/38	High, high
55	60 (39, 21)	Mean, 13.5	None None	PRED 1 for 10 days, tapered off over next 4 days Placebo	CT scan after 6 months, 9 months' total follow-up at 1-month intervals	4/30 14/30	16/30 14/30	Low, low
57	52 (36, 16)	Mean, 16	None None	Intravenous methylpred at 1 g/1.72 m^2 per day for 5 days None	CT scan after 2 months, 9 months' total follow-up at 1-month intervals	4/25 9/27	15/25 5/27	High, high
59	100	NR	None None	PRED 1 for 10 days Placebo	CT scan after 2–3 months, 12 months' total follow-up	5/47 12/45	32/47 26/45	High, high
58	90 (52, 38)	Mean, 19.3	ALB, 15 days None	PRED 1 for 2 weeks, tapered off over next 3 days PRED 1 for 2 weeks, tapered off over next 3 days	CT scans after 1 and 6 months, 6 months' total follow-up at 1-month intervals	9/48 5/42	33/45 25/36	High, high

60	53 (28, 15)	Mean, 24	ALB, 2 weeks None	None None	CT scans after 1, 3 and 6 months, 6 months' total follow-up	3/23 4/20	22/23 14/20	High, high
61	103 (59, 44)	Mean, 19.6	ALB, 4 weeks None	None None	MRI after 3, 6 and 12 months, 6 months' total follow-up	7/50 5/53	10/45 9/48	High, high
63	67 (43, 24)	Mean, 17	ALB, 3 days Placebo	None None	CT scan after 6 months, 6 months' total follow-up	3/33 1/34	28/33 14/34	High, high
62	148 (104, 44)	Mean, 19	None None	PRED at 40–60 mg/day for 2 weeks, tapered off within next 4 days Placebo	CT scan after 3 months, MRI after 6 months, 9 months' total follow-up at 3-month intervals	16/73 19/75	28/60 21/54	Low, high

NA: not applicable; NR: not reported; PRED: prednisolone

[a] In all studies, the dose of ALB was 15 mg/kg body weight per day. The dose of prednisolone is given in mg/kg bw per day, unless otherwise indicated. All patients received AED monotherapy (phenytoin or carbamazepine).

[b] The first assessment was for seizure recurrence and the second for lesion resolution.

Fig. A4.3.1. Graphical presentation of the effects of intervention[1]

Seizure recurrence			
Albendazole + corticosteroid	0.69 (0.27, 1.83)	0.48 (0.11, 1.81)	**0.32 (0.10, 0.93)**
	Corticosteroid	1.44 (0.44, 5.51)	0.46 (0.19, 1.01)
Between-study variance: 0.54		Albendazole	0.66 (0.22, 2.17)
Posterior mean residual deviance: 26.77[a]			Conservative treatment
Lesion resolution			
Albendazole + corticosteroid	1.17 (0.38, 3.55)	1.31 (0.58, 3.00)	**3.05 (1.24, 7.95)**
	Albendazole	1.13 (0.43, 3.05)	**2.63 (1.61, 6.34)**
Between-study variance: 0.54		Corticosteroid	**2.32 (1.20, 4.75)**
Posterior mean residual deviance: 26.77[b]			Conservative treatment

The limitations of the study by Zhao et al. *(48)* are:

- comparison of different therapeutic schedules;
- different durations of drug administration;
- different drugs (e.g. corticosteroids);
- different comparison groups within studies compared for all studies;
- different follow-up times;
- different age groups (adults and children);
- not all patients had SELs; and
- no analysis of confounding or interaction.

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[1] Pooled odds rations for seizure recurrence and lesion resolution in Bayesian network meta-analysis. In each cell, odd rations (with 95% credible intervals) are the pooled effects of the intervention labelled horizontally to the left of the plot compared with the intervention labelled vertically below. Results with statistical significance are shown in bold type.
[a] Compared with 27 data points.
[b] Compared with 29 data points.
Source: reference *48*

Furthermore, Zhao et al. *(48)* concluded from the network meta-analysis that use of ALB and corticosteroids combined significantly decreased the risk of seizure recurrence for individuals with SEL when compared with symptomatic treatment (mainly AEDs) (odds ratio, 0.32; 95% CI, 0.10;0.93). ALB and corticosteroids alone tended to reduce the risk of seizure relapse, but the effect was not statistically significant.

ALB and corticosteroids resulted in better outcomes with regard to lesion resolution than conservative treatment. ALB alone and corticosteroids alone also resulted in better lesion resolution than symptomatic treatment.

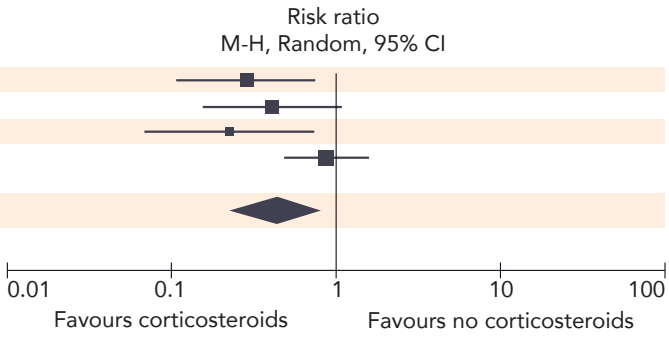
Otte et al. *(49)* performed a standard meta-analysis of 15 RCTs in a systematic review. They included two additional references, Alarcón et al. *(34)* and Pretell et al. *(64)* but omitted Sharma et al. *(58)*. They also concluded that anthelmintic treatment increases the rate of seizure cessation, and the effect was consistent for cyst resolution. Corticosteroids reduced the risk of seizure events at 6 months of follow-up, although the effect was not statistically significant after 1 year of follow-up. Granuloma resolution was favoured by corticosteroid treatment but was not statistically significant. Otte et al. *(49)* did not present a separate analysis of the effect of anthelmintic drugs plus corticosteroids versus other schedules such as anthelmintic therapy alone, corticosteroids alone or controls.

The results of the three additional studies identified by our search support the results of Zhao et al. *(48)* and Otte et al. *(49)*.

Fig. A4.3.2 shows our results for PICO 5 from the studies included in the meta-analysis and the pooled estimate for the effectiveness of anti-inflammatory treatment on the cumulative incidence of seizure recurrence.

Fig. A4.3.2. Forest plot of comparison: corticosteroids versus no corticosteroids. Outcome: seizure recurrence

	Corticosteroids plus AED		AED			Risk ratio
Reference	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
55	4	30	14	30	23.1%	0.29 (0.11, 0.77)
59	5	50	12	50	23.6%	0.42 (0.16, 1.10)
54	3	49	13	48	18.8%	0.23 (0.07, 0.74)
62	16	73	19	75	34.6%	0.87 (0.48, 1.55)
Total		202		203	100%	0.44 (0.23, 0.85)
Total events	28		58			



Heterogeneity: Tau^2 =0.25; Chi^2=6.56, df=3 (P=0.09); I^2 =54%

Test for overall effect: Z=2.43 (P=0.02)

Source: reference *48*

M-H, Mantel–Haenszel test

Quality assessment

The studies included in question 4 were found to be of low quality for lesion resolution and very low quality for seizure recurrence according to the GRADE criteria as evaluated by Zhao et al. *(48)*. Low is defined as "confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect", and very low is defined as "very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect" (Table A4.3.2).

Table A4.3.2. GRADE table for PICO question 4

Effects and confidence in the estimate of effects				
Patients or population: Patients with single enhancing lesion NCC Settings: Outpatient and/or hospitalized patients Interventions: Albendazole+Corticosteroid, Corticosteroid, Albendazole Comparison: Corticosteroid, Albendazole, Antiepileptic (Conservative)				
Outcome				
	Albendazole + Corticosteroid	Coticosteroid	Albendazole	Comments
Seizure recurrence				
Corticosteroid	OR: 0.69 (0.27, 1.18)			
Albendazole	OR: 0.48 (0.11, 1.81)	OR: 1.44 (0.44, 5.51)		
Antiepileptic	OR: 0.32 (0.10, 0.93)	OR: 0.46 (0.19, 1.01)	OR: 0.66 (0.22, 2.17)	
Grade of evidence	●○○○ Very low Due to: (1) [*1] Serious risk of bias [unclear method of allocation, lack of blinding in more than half of the studies] (2) [*1] Some uncertainty about directness, because generalizability is compromised given that all are Indian patients (3) [*1] Imprecision Based on 1066 participants (13 studies)			
Lesion resolution				
Corticosteroid	OR: 1.31 (0.58, 3.00)		1.13 (0.43, 3.05)	
Albendazole	OR: 1.17 (0.38, 3.55)			
Antiepileptic	OR: 3.05 (1.24, 7.95)	OR: 2.32 (1.20, 4.75)	2.63 (1.61, 6.34)	
Grade of evidence	●●○○ Low Due to: (1) [*1] Serious risk of bias [unclear method of allocation, lack of blinding in more than half of the studies] (2) [*1] Some uncertainty about directness, because generalizability is compromised given that all are Indian patients Based on 1073 participants (14 studies)			

Source: reference *48*

The GRADE assessment rated the evidence for use of corticosteroids as moderate because of downgrading for indirectness (Table A.4.3.3).

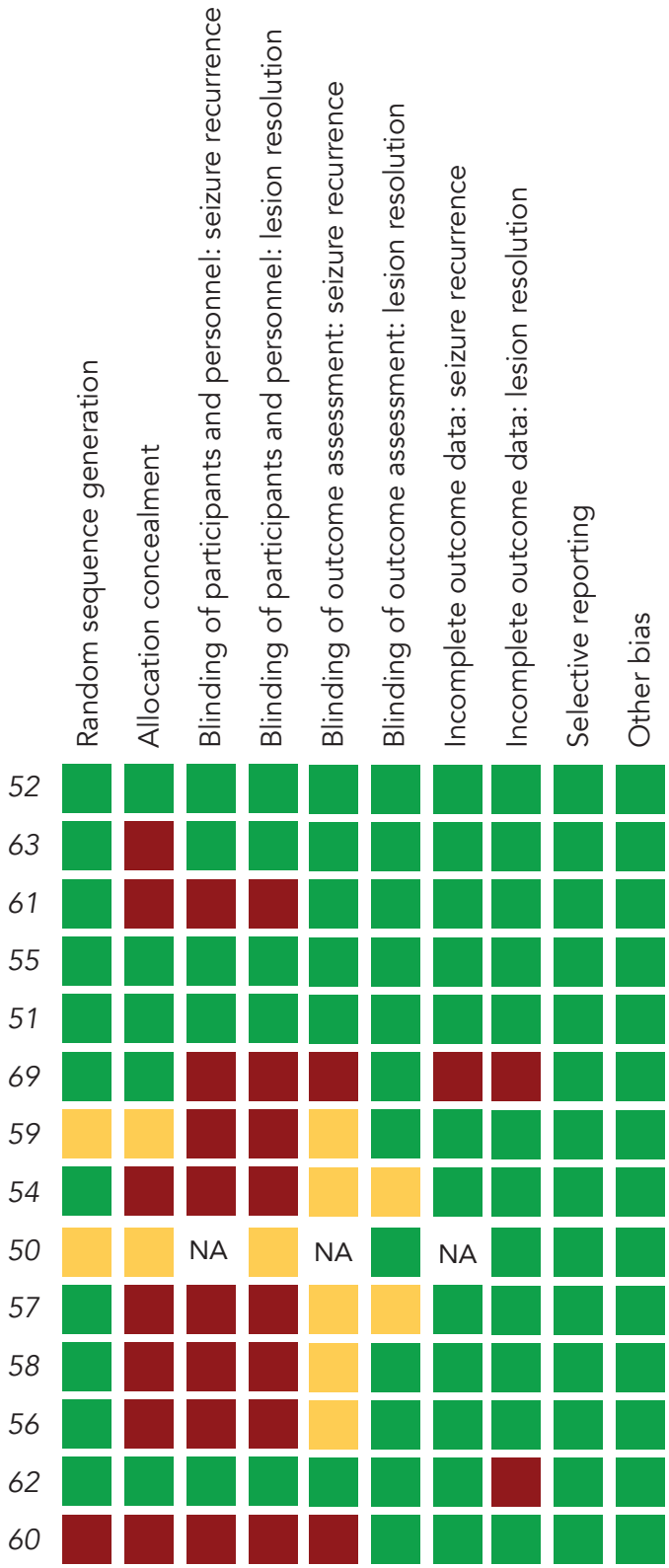
Table A4.3.3. GRADE Table for PICO question 5: Anti-inflammatory treatment plus AED treatment compared to AED treatment alone or with placebo in individuals with SEL neurocysticercosis

Certainty assessment							Summary of findings				
N° of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Others: publication bias	Quality of evidence	Study event rate (%)		Relative effect (95% CI)		
							With AED treatment alone or with placebo	With anti-inflammatory treatment plus AED treatment		Risk with AED treatment alone or with placebo	Risk difference with anti-inflammatory treatment plus AED treatment
Outcome: Seizure recurrence (follow-up: 6-12 months)											
405 (4 RCTs)	Serious	Not serious	Serious[a]	Not serious	None	●●○○ Low	58/203 (28.6%)	28/202 (13.6%)	RR 0.44 (0.23–0.85)	286 per 1000	160 fewer per 1000 (220–43 fewer)

[a] Differences in interventions (applicability)

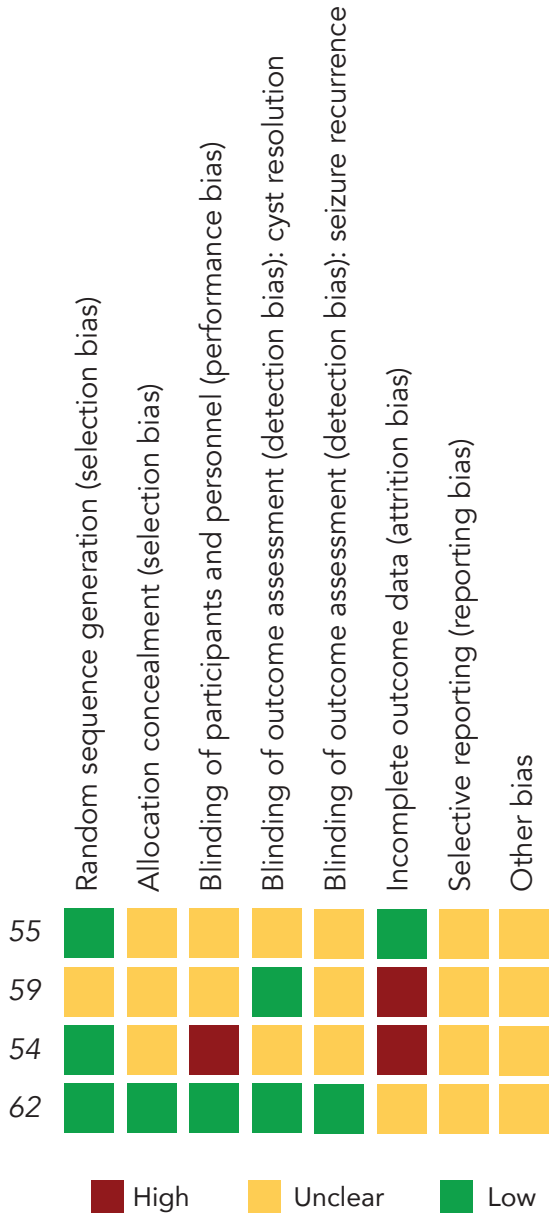
The risks of bias for question 4 as assessed by Zhao et al. *(48)* are shown in Fig. A4.3.3, and for question 5 in Fig. A4.3.4.

Fig. A4.3.3. Risks of bias for question 4



Source: reference *48*

Fig. A4.3.4. Risks of bias for question 5



Source: reference *48*

Evidence to recommendations

4	In individuals with symptomatic neurocysticercosis with a SEL, is anthelmintic therapy associated with better clinical outcomes than symptomatic treatment alone?
5	In individuals with symptomatic neurocysticercosis with a SEL, is anti-inflammatory therapy associated with better clinical outcomes than AED treatment alone?
Factor	Explanation
Narrative summary of evidence base	One meta-analysis was found of 14 studies. ALB and corticosteroids combined significantly decreased the risk of seizure recurrence in individuals with SEL (odds ratio, 0.32; 95% CI, 0.10;0.93) as compared with symptomatic treatment. ALB alone did not significantly reduce this risk (odds ratio, 0.66; 95% CI, 0.22;2.17). ALB and corticosteroids were a better option than conservative treatment for lesion resolution (odds ratio, 3.05; 95% CI, 1.24;7.95). ALB alone also resulted in better lesion resolution than symptomatic treatment (odds ratio, 2.63; 95% CI, 1.61;6.34). An additional three studies were found that were not included in the meta-analysis, which support the results of the meta-analysis. Treatment with corticosteroids was more beneficial than no corticosteroid treatment (RR, 0.44; 95% CI , 0.23; 0.85). Side-effects of corticosteroids were not addressed. A major gap in all the studies is the very short follow up (most had a follow-up of 6 months to 1 year, and the longest was 18 months). Seizure outcome cannot be evaluated conclusively during such a short follow-up, as recurrences can occur for several years after the SEL has resolved.
Summary of the quality of evidence	The quality of the evidence was graded as low for the effect of anthelmintic therapy on cyst resolution and very low for the effect of anthelmintic therapy on seizure control in individuals with symptomatic neurocysticercosis and a SEL. The evidence for treatment with corticosteroids of individuals with symptomatic neurocysticercosis with SEL was graded as moderate because of downgrading for indirectness.
Balance of benefits and harms	No expert opinion could be given on whether the benefit of treatment (ALB in combination with corticosteroids) of individuals with symptomatic neurocysticercosis with a SEL outweighs the harm. Side-effects were not analysed or mentioned in the above studies, although side-effects have been reported in a small number of patients receiving ALB in combination with corticosteroids *(70)*.

Values and preferences, including any variability and human rights issues	From the perspective of people with epilepsy or seizures, the factors in favour of anthelmintic treatment of symptomatic individuals with SEL are the: importance of the intervention for better seizure control; the importance of the intervention for better cyst resolution; and the importance of the outcomes for better social functioning and less stigmatization and discrimination. The factors against anthelmintic treatment of symptomatic individuals with SEL are the: importance of adverse events due to the intervention; importance of economic loss due to hospitalization for interventions; and importance of the lack of availability of neuroimaging facilities.
Costs and resource use and any other relevant feasibility issues	Availability and price of anthelmintic therapy (on WHO List of Essential Medicines) Access to and costs of neuroimaging, which is standard practice before initiation of anthelmintic medication with corticosteroids Training of clinical personnel

Final recommendation(s)

Anthelmintic therapy (ALB) in combination with corticosteroids should be provided to individuals with symptomatic neurocysticercosis and a SEL for better outcomes in terms of cyst resolution and potentially improved seizure control.

Clinical and regional consideration(s)

Although no systematic review was found, the clinical experience of experts indicates that anthelmintic drugs should not be used in patients with pronounced inflammation or increased intracranial pressure. These patients should be managed with corticosteroids alone.

Research gap(s)

What is the optimal drug(s), dose, duration and combination of anthelmintic therapy for individuals with symptomatic neurocysticercosis and a SEL?

What is the effect of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) on seizure severity and frequency, long-term seizure recurrence and reduced duration of AED therapy in individuals with symptomatic neurocysticercosis and a SEL?

What are the adverse events of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) in individuals with symptomatic neurocysticercosis and a SEL?

What is the optimal drug, dose and duration of anti-inflammatory therapy (corticosteroids) in individuals with symptomatic neurocysticercosis and a SEL?

What is the effect of corticosteroid therapy alone on seizure severity and frequency, long-term seizure recurrence and reduced duration of AED therapy in individuals with symptomatic neurocysticercosis and a SEL?

What are the adverse events of corticosteroid therapy alone in individuals with symptomatic neurocysticercosis and a SEL?

Conduct a meta-analysis of the homogeneous studies identified in systematic reviews and meta-analyses on use of anthelmintic therapy in individuals with symptomatic neurocysticercosis and a SEL.

Strength of recommendation(s)

Conditional. The recommendation was made conditional because of the heterogeneity among studies and the limited effect. Nevertheless, all the studies indicated that the combination of ALB and corticosteroids has a beneficial effect.

Additional remarks

Many studies were available on the use of anthelmintic therapy in combination with corticosteroids in individuals with a SEL; however, significant limitations were found to the synthesis of these data.

Evidence was not retrieved on use of ALB in pregnant women or children, for whom expert advice should be sought.

EVIDENCE PROFILE: QUESTION 6

6	In individuals with a neurocysticercosis SEL and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Population	Individuals with a SEL and epilepsy
Intervention	Prolonged administration of AEDs
Comparator	Shorter regimens of AEDs
Outcome	Fewer episodes of seizure relapse or more frequent achievement of seizure-free status

Background

AEDs are used in the treatment of epilepsy due to neurocysticercosis, and the duration of therapy is based on expert opinion or consensus. Monotherapy with carbamazepine or phenytoin is the most common choice for seizure control, although a small proportion may require polytherapy *(47)*. There is no consensus on the optimal length of AED therapy in patients with a SEL and epilepsy, and there are few systematic data to support withdrawal of AED *(70–74)*. In this systematic review, we evaluated whether prolonged administration of AEDs (at least 2 years) is associated with better clinical outcomes than shortened regimens in individuals with SEL and epilepsy.

Inclusion and exclusion criteria

The search strategy and results are given in Annex 3 and section 2.3.2 (Fig. 3), respectively.

INCLUSION CRITERIA:	
Types of study:	Experimental and observational studies
Types of participant:	Individuals with SEL neurocysticercosis on MRI or CT scan with a well-established diagnosis of epilepsy
Types of intervention:	The intervention group may have received any of the currently marketed AEDs, in addition to the usual treatment for neurocysticercosis (anthelmintics or corticosteroids or both). The controls may have received AEDs for a shorter duration, given either singly (monotherapy) or in combination.
Types of outcome measures:	Seizure recurrence over a specific time.
Exclusion criteria:	Case series and case reports and neurocysticercosis patients other than those with a SEL were excluded.

Summary of findings

Four studies were included for question 6 (Table A4.4.1).

Table A4.4.1. Summary of studies included and main findings for question 6

Reference	Participants	AED	Duration of treatment
72	81 patients Group A: 41 Group B: 40	Not available	Group A: 6 months Group B: 1 year
73	106 children Group A: 55 Group B:51	Carbamazepine (n=85), Phenytoin (n=19)[a]	Group A: 1 year Group B: 2 years
71	73 patients Group A: 47 Group B: 26	Carbamazepine (n=38) Phenytoin (n=35)	Group A: 6 months Group B: 2 years
74	206 patients Group A: 98 Group B: 108	Carbamazepine (n=176), Phenytoin (n=51)[b]	Group A: 6 months Group B: 2 years

[a] Numbers do not add up, as information on two children was missing.

[b] Numbers do not add up, and there was no further information on whether patients were given mono- or combination therapy

Gupta et al. *(72)* studied 81 people with epilepsy and a cerebral SEL to evaluate the effect of treatment with AED for either 6 or 12 months; the patients were followed for 1 year after stopping treatment. About 12% of patients in both groups had seizure relapses after AED withdrawal, all cases within the first 6 months of stopping treatment. As four of the five relapses in the two groups were observed in people with residual calcification, the authors concluded that persistent or residual calcified lesion might require longer AED treatment. The proportion of patients with calcifications among those who did not have seizure relapse was not reported, and the association cannot be confirmed.

A similar study was performed by Singhi et al. *(73)* in 106 children with a SEL and seizures who were allocated to receive one (n=55) or two (n=51) years of AEDs. After stopping AEDs, the patients were followed for 1 year. Three patients in each group had seizure relapses during the follow-up, and these events were strongly associated with calcified lesions or an abnormal electroencephalogram at the time of AED withdrawal (RR, 26.2; "P = 0.003"). Thussu et al. *(71)* also evaluated patients presenting with seizures and a SEL given AED for 6 months (n=47) or 2 years (n=26). The patients were followed for 1 year after AED withdrawal. Non-significant differences in seizure relapse were found between the two groups: 17% (8/47) among those treated for 6 months and 11.5% (3/26) among those treated for 2 years. As reported by Singhi et al. *(73)*, the subset of patients with residual calcification were more likely to present with recurrence of seizures than patients with total resolution.

Verma et al. *(74)* also compared 6 months (n=98) with 2 years (n=108) of AED therapy in people with a SEL. The patients were followed for at least 18 months. The authors analysed the results separately for people without residual calcification and for those with punctuated residual calcified lesions. Recurrence of seizures was more frequent in people with calcified scars who received a short scheme of AEDs than in patients with residual calcification and 2 years of therapy, i.e. 42.2% versus 21.7% (Z, 1⁄4 1.97; "P < 0.05").

An observational study by Rajshekhar and Jeyaseelan *(47)* demonstrated a recurrence of seizures in about 15% of patients with a SEL after early withdrawal of AEDs. Risk factors for seizure recurrence included having had more than two seizures or breakthrough seizures and a follow-up CT scan showing a calcific residue of the granuloma. It was concluded that AED therapy might have to be continued for longer in patients with these risk factors.

Only one study reported no side-effects, whereas this information was not available in the other studies.

Graphical presentation of effects of intervention

Figs A4.4.1 and A4.4.2 show the results of the studies included in the meta-analysis and the pooled estimate of the effectiveness of different AED regimens on the cumulative incidence of seizure recurrence (6 months versus 12–24 months and 6–12 versus 24 months).

Fig. A4.4.1. Forest plot of comparison of 6 months versus 12–24 months of AED treatment. Outcome: seizure recurrence.

Comparison: 6 months of AED treatment versus 12–24 months of AED treatment

	6 months AED		12–24 months AED			Risk ratio
Reference	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
72	5	41	5	40	20.8%	0.98 (0.31, 3.11)
71	8	47	3	26	18.3%	1.48 (0.43, 5.08)
74	16	98	13	108	60.9%	1.36 (0.69, 2.67)
Total (95% CI)		186		174	100%	1.29 (0.76, 2.18)
Total events	29		21			

Heterogeneity: Tau^2 =0.00; Chi^2=0.29, df=2 (P=0.87); I^2 =0%

Test for overall effect: Z=0.93 (P=0.35)

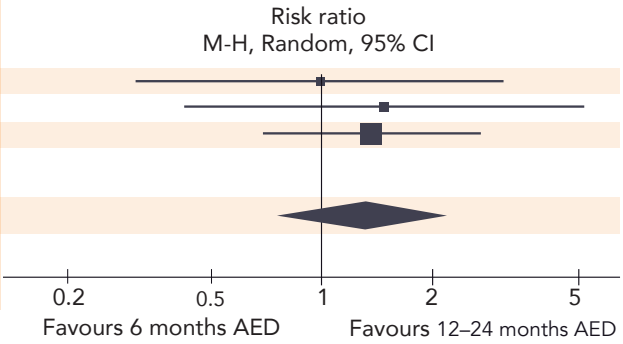


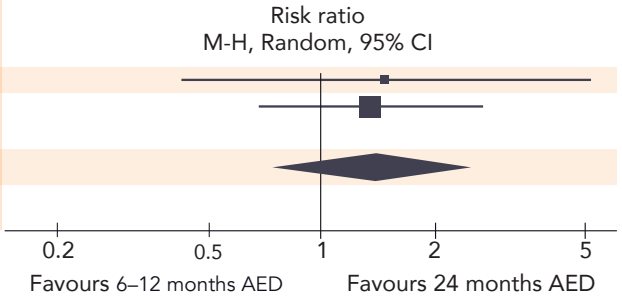
Fig. A4.4.2. Forest plot of comparison of 6–12 months of AED treatment versus 24 months of AED treatment. Outcome: seizure recurrence.

Comparison: 6–12 months of AED treatment versus 24 months of AED treatment

	6–12 months AED		24 months AED			Risk ratio
Reference	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
71	8	47	3	26	23.1%	1.48 (0.43, 5.08)
74	16	98	13	108	76.9%	1.36 (0.69, 2.67)
Total (95% CI)		145		134	100%	1.38 (0.76, 2.51)
Total events	24		16			

Heterogeneity: Tau^2 =0.00; Chi^2=0.01, df=1 (P=0.91); I^2 =0%

Test for overall effect: Z=1.07 (P=0.29)



Effects of intervention in patients who present with residual calcification lesion

All four studies reported the 1-year cumulative incidence of seizure relapse in patients with calcification or persistent lesions. The cumulative incidence of relapse among these patients in each study was calculated in three of the studies as shown in Table A4.4.1.

Table A4.4.1. Cumulative incidence of seizure relapse in patients

Reference	With residual or calcified lesions	Without residual or calcified lesions
71	32.4% (11/34)	0 % (0/39)
73	15.0% (6/40)	0 % (0/60)
74	30.4% (24/79)	3.9% (5/127)

In the study of Singhi et al. *(73)*, three patients included in the numerator had calcified lesions, and the other three had persistent lesions, while the lesions were not specified for the 40 patients in

the denominator. In the studies of Thussu et al. and Verma & Misra, there were only participants with calcification in the denominators.

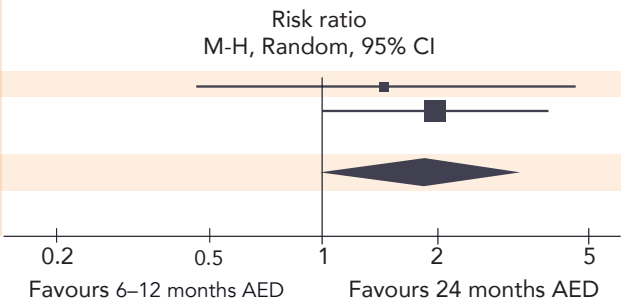
The effect of 6 months versus 24 months of AED could be analysed in two studies: Thussu et al. *(71)* and Verma & Misra *(74)*. The longer schedule was protective effect against new seizures in patients whose cyst had calcified (Fig. A4.4.3).

Fig. A4.4.3. Forest plot of comparison: 6 months' AED treatment versus 24 months' AED treatment. Outcome: seizure recurrence.

	6 months AED		24 months AED			Risk ratio
Reference	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
71	8	22	3	12	31.7%	1.45 (0.47, 4.48)
74	14	33	10	46	68.3%	1.95 (0.99, 3.84)
Total (95% CI)		55		58	100%	1.79 (1.00, 3.20)
Total events	22		13			

Heterogeneity: Chi^2=0.19, df=1 (P=0.66); I^2 =0%

Test for overall effect: Z=1.98 (P=0.05)



Conclusion

We evaluated the results as a risk ratio and found no significant differences in either schedule: 6 months vs 12–24 months or 6–12 months vs 24 months (RR, 1.29; 95% CI, 0.76; 2.18; and RR, 1.38; 95% CI, 0.76;2.51, respectively).

The three studies included in the meta-analyses suggested that seizure recurrence was correlated with persistent and calcified lesions, and we were able to estimate the cumulative incidence of seizure relapse in two of the studies *(71, 74)*. When we considered only patients with residual calcification, we found that longer schedules may protect against further seizure relapse.

Quality assessment

The studies on AED therapy of both short (6 months) and longer (6–12 months) duration were found to be of low quality according to the GRADE criteria; however, the evidence from the sub-group analysis of patients whose cysts had calcified was graded as moderate, as it was adjusted for the different patient groups (Table A4.4.2). Fig. A4.4.4 shows the risk of bias for question 6.

Fig. A4.4.4. Risk of bias for question 6

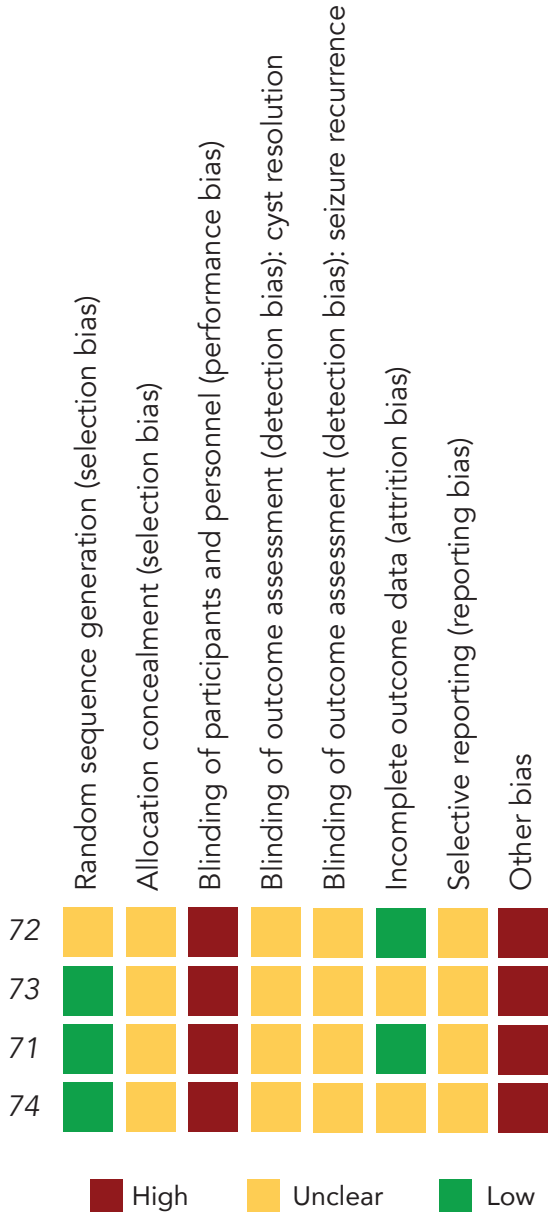


Table A4.4.2. GRADE table for PICO question 6: comparison of 6 or 6–12 months with 12–24 or 24 months of AED treatment for individuals with SEL neurocysticercosis

Quality assessment							Summary of findings				
No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Others: Publication bias	Quality of evidence	Study event rates (%) 12–24 or 24 months of AED treatment	Study event rates (%) 6 or 6–12 months of AED treatment	Relative effect (95% CI)	Anticipated absolute effects: Risk with 12–24 or 24 months of AED treatment	Anticipated absolute effects: Risk difference with 6 or 6–12 months of AED treatment
Outcome: Seizure recurrence after 6 months as compared with 12–24 months of AED treatment											
360 (3 RCTs)	Serious[a]	Not serious	Serious[b]	Not serious	None	⨁⨁ Low	21/174 (12.1%)	29/186 (15.6%)	RR, 1.29 (0.76; 2.18)	121/1000	35 more per 1000 (29 fewer to 142 more)
Outcome: Seizure recurrence after 6–12 months as compared with 24 months of AED treatment											
279 (2 RCTs)	Serious[a]	Not serious	Serious[b]	Not serious	None	⨁⨁ Low	16/134 (11.9%)	24/145 (16.6%)	RR, 1.34 (0.76;2.51)	119/1000	41 more per 1000 (29 fewer to 180 more)
Outcome: Seizure recurrence after 6 months as compared with 24 months of AED treatment in patients whose cysts had calcified											
113 (2 RCTs)	Serious[a]	Not serious	Not serious	Not serious	None	⨁⨁⨁ Moderate	13/58 (22.4%)	24/55 (43.6%)	RR, 2.00 (1.14;3.52)	224/1000	224 more per 1000 (31 more to 565 more)

Based on references *36*, *37*, *75* and *76*

[a] Overall high risk of bias of included studies

[b] Differences in populations

Evidence to recommendations

6	In individuals with a neurocysticercosis SEL and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Factor	Explanation
Narrative summary of the evidence base	No significant differences were found in comparisons between 6 months and 12–24 months or between 6–12 months and 24 months of therapy (RR, 1.29; 95% CI, 0.76 ; 2.18 and RR, 1.38; 95% CI, 0.76 ; 2.51, respectively). Two studies suggested that seizure recurrence was correlated with calcified lesions (RR, 1.79; 95% CI, 1.00 ; 3.20. No side-effects were reported in the only study in which adverse events were recorded.
Summary of the quality of evidence	The quality of the evidence was graded as low for seizure recurrence after 6 months as compared with 12–24 months of AED treatment and after 6–12 as compared with 24 months of AED treatment, whereas the evidence was graded as moderate for seizure recurrence after 6 months as compared with 24 months of AED treatment in individuals with a SEL neurocysticercosis whose cysts had calcified.
Balance of benefit and harms	No conclusion could be reached about whether prolonged AED therapy in individuals with a SEL and epilepsy outweighs the harm, as the side-effects of AED could not be analysed because of lack of information. It was assumed that the side-effects are similar to symptoms in other people with epilepsy and depend on the drug, dose and duration of treatment. See also "research gaps" below. Individuals with a SEL and epilepsy who undergo prolonged AED therapy may, however, incur disproportionate out-of-pocket expenditure.
Values and preferences, including any variability and human rights issues	Importance of the intervention for better seizure control Importance of the outcomes for better social functioning and less stigmatization and discrimination Importance of adverse events due to intervention
Costs and resource use and any other relevant feasibility issues	Availability and price of AEDs (on the WHO List of Essential Medicines) Costs of prolonged treatment with AEDs Training of clinical personnel
Final recommendation(s) Withdrawal of AEDs should be considered 6 months after the last seizure in individuals with a SEL and epilepsy who have a low risk of seizure recurrence (defined as patients with a resolved granuloma, no residual calcification and who are seizure free). AED therapy should be continued in people with an SEL that persists on neuroimaging and those that resolve with residual calcification. Remarks: There is limited evidence about the optimal duration of AED therapy for a SEL; however, the optimal duration appears to be a few weeks after complete resolution of the SEL.	

Clinical and regional consideration(s)

No studies were available on patients with a SEL and epilepsy and shortened AED therapy in countries other than India, although anecdotal data from Latin America support the published findings.

Research gap(s)

What is the optimal drug(s), dose and duration of AED therapy in individuals with a SEL and epilepsy?

What are the side-effects of AED therapy in individuals with a SEL neurocysticercosis lesion and epilepsy?

Strength of recommendation(s)

Conditional – The recommendation was made conditional because limited evidence was available. In addition, the morbidity and costs associated with continuous AED drug treatment in patients with a SEL and epilepsy who have no risk factors for seizure recurrence (i.e. patients with a resolved granuloma, no residual calcification and who are seizure free for at least 3 months *(47)*) in LMIC may outweigh the benefit of continuous AED therapy.

Additional remarks

Many factors influence seizure recurrence in patients with epilepsy. For other considerations on managing epilepsy, see the WHO guidelines on epilepsy management.

EVIDENCE PROFILE: QUESTION 7

7	In individuals with single or multiple calcified cysticercal lesion(s) and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Population	Individuals with calcified neurocysticercosis lesion(s) and epilepsy
Intervention	Prolonged administration of AEDs
Comparator	Shortened regimens of AEDs
Outcome	Fewer episodes of seizure relapse, or more frequent achievement of seizure-free status

Background

Neurocysticercosis remains a major challenge in public health because of the associated secondary epilepsy *(2, 76, 77)*, and it is the single most important cause of acquired epilepsy in poor and rural areas and probably the world. Most of the disease burden (80%) is that of people living in LMICs *(78)*.

T. solium larvae establish themselves in the brain parenchyma as viable cysts. As part of their natural life cycle or subsequent to anthelmintic treatment, these cysts degenerate and either

resolve completely or leave a small calcified lesion in the parenchyma *(4)*. Brain calcification is commonly found in areas endemic for cysticercosis. In the general population, the proportion of asymptomatic individuals with calcified neurocysticercosis ranges from 5% to 25% *(79, 80–82)*. In hospital-based studies, neurocysticercosis also represents a primary cause of secondary epilepsy in endemic areas *(83–86)*.

Cerebral calcifications can persist in the host's brain for many years, and, in endemic areas, these calcifications have been associated with seizures in population-based studies. Although calcified neurocysticercosis has a major role in seizure burden, the causal factors involved in the calcification process and the physiopathology of epileptic seizures in patients with calcified lesions are still inadequately understood *(87)*. The proportion of viable and degenerating cysts that results in calcified scars ranges from 20% to 60% *(36, 37)*; however, the mechanisms involved in the calcification process have not been elucidated. It is still unknown why some cysts progress to calcified lesions while others completely resolve.

The incidence of seizure relapse in patients with calcified neurocysticercosis and epilepsy has been inadequately studied. Nash and collaborators reported an incidence of 35.6 per 100 person-years, but, because of a limited sample size, they could not explore the risk factors associated with seizure relapse *(75)*. Patients with epilepsy and calcified neurocysticercosis typically remain under AED treatment for several years, and the drug is gradually withdrawn after 2–3 years without seizures; however, some of these patients will experience seizure relapse. This systematic review was conducted to evaluate the evidence to determine whether prolonged administration of AEDs (at least 2 years) is associated with less seizure relapse than shortened regimens.

Inclusion and exclusion criteria

The search strategy and results are given in Annex 3 and section 2.3.2 (Fig. 3), respectively.

INCLUSION CRITERIA:	
Types of studies:	Experimental and observational studies
Types of participants:	Individuals with calcified neurocysticercosis with a well-established diagnosis of a seizure disorder
Types of intervention:	The intervention group may have received any of the currently marketed AEDs. The control group may have received the same AED for a shorter duration. The AEDs may have been given singly (monotherapy) or in combination.
Types of outcome measures:	Incidence rate or seizures, cumulative incidence of seizures, time to next seizure
Exclusion criteria:	We excluded case series and case reports and studies of patients with neurocysticercosis other than with calcified lesions.

Summary of findings

No publication was found on various durations of AED treatment in patients with calcified neurocysticercosis; however, we identified three additional papers on the topic of AED and calcified neurocysticercosis *(76, 88, 89)*. In the additional papers, the cumulative incidence of seizure relapse after AED discontinuation in people with 2 years free of seizures under AEDs was high, with more than 80% of patients relapsing in the first 6 months after AED discontinuation, even if withdrawal was gradual. See Table A4.5.1 for an overview of the main findings.

Table A4.5.1. Main findings on the relapse rate in patients with calcified neurocysticercosis in the additional studies identified for question 7

Ref.	Country	Participants	Previous anthelmintic treatment	Study design	Follow-up time after AED withdrawal	Relapse rate	Length seizure-free before AED withdrawal	AED tapering off
76	Ecuador	Adults n=11	100%	Prospective cohort	12 months	90.9% (10/11)	2 years	6–8 weeks
88	Ecuador	Adults n=30	50%	Prospective cohort	12 months	83.3% (25/30)	2 years	NA
89	India	Adults n=8	NA	Prospective cohort	6 months	100% (8/8)	2 years	3 months

NA, not available

Del Brutto *(76)* reported on 40 neurocysticercosis patients with epilepsy who were prospectively followed from the time of diagnosis until 12 months after AED withdrawal. Of the 40 patients treated with ALB, 11 presented with well-defined parenchymal calcification at follow-up CT scan at month 3. After the patients had been free of seizures for 2 years and AEDs were tapered off, 10 of 11 patients with calcified neurocysticercosis had seizure relapse. The aim of the study was to evaluate different prognostic factors for seizure recurrence (for example, CT scan, electroencephalogram, type of seizure). Univariate analysis of these factors showed that brain calcification was significantly associated with seizure relapse. The author suggested that patients with residual calcifications and those with recurrent seizures and multiple cysts are at a higher risk of seizure relapse after AED withdrawal.

In a study by Del Brutto & Campos *(88)*, 30 patients with parenchymal cysts were followed prospectively from diagnosis until 12 months after AED withdrawal. The patients were classified in two groups: neurocysticercosis patients who had developed calcifications after treatment with ALB and patients in whom calcification of the parenchymal brain cysts was due to spontaneous transformation. Both groups had been free of seizures for 2 years when AED withdrawal started. The two groups had a similar cumulative incidence of seizure relapse in the first 6 months (13/15 and 12/15 patients), suggesting that the risk of seizure recurrence is not related to previous ALB treatment.

Naranya & Pati *(89)* reported on eight patients with seizures and calcified lesions, for whom AED were tapered off over 3 months once they had been free of seizures for 2 years. All the patients relapsed within 6 months. The authors concluded that longer AED treatment might be required for neurocysticercosis patients with calcified lesions.

Quality assessment

As the three additional studies did not meet the inclusion criteria for question 7, GRADE and quality of evidence assessment is not applicable.

Evidence to recommendations

7	In individuals with single or multiple calcified cysticercal lesion(s) and epilepsy, is prolonged administration of AEDs (at least 2 years) associated with better clinical outcomes than shorter regimens?
Factor	Explanation
Narrative summary of the evidence base	No study was identified of various durations of AED treatment in individuals with single or multiple calcified cysticercal lesion(s) and epilepsy. Three additional papers were identified on seizure relapse after withdrawal of AED in individuals with single or multiple calcified cysticercal lesion(s) and epilepsy. Even after a 2-year seizure-free interval, the relapse rate was as high as 83.3–100% in individuals with single or multiple calcified cysticercal lesion(s) and epilepsy 6–12 months after withdrawal of AED.
Summary of the quality of the evidence	The quality of the evidence cannot be summarized because of lack of evidence (very low).
Balance of benefit and harms	Whether the benefit of prolonged AED therapy in individuals with single or multiple calcified cysticercal lesions and epilepsy outweighs the harm cannot be ascertained, as side-effects of AED could not be studied due to lack of information.
Values and preferences including any variability and human rights issues	Importance of the intervention for better seizure control Importance of the outcomes for better social functioning and less stigmatization and discrimination Importance of adverse events due to the intervention
Costs and resource use and any other relevant feasibility issues	Availability and price of AED (on the WHO List of Essential Medicines) Costs of prolonged treatment with AED Training of clinical personnel
Final recommendation(s) AED therapy should be continued for at least 2 years in people with single or multiple calcified neurocysticercosis and epilepsy. These patients should be closely monitored if treatment is withdrawn. Further recommendations on discontinuation of AED can be found in WHO's mhGAP Intervention Guide *(90)*.	
Clinical and regional consideration(s) The treatment guidelines of the International League against Epilepsy should be consulted as long as there is no evidence for the use of prolonged AED therapy in individuals with single or multiple calcified cysticercal lesions and epilepsy.	

Research gap(s)

What is the optimal drug(s), dose and duration of AED therapy in individuals with single or multiple calcified cysticercal lesions and epilepsy?

What are the side-effects of AED therapy in individuals with single or multiple calcified cysticercal lesions and epilepsy?

Strength of recommendation(s)

Conditional – The recommendation was made conditional because of lack of evidence. There is, however, consensus in the epilepsy treatment guidelines of the International League against Epilepsy that epilepsy due to brain lesions requires continued treatment with AED *(91, 92)*. In addition, the morbidity and cost associated with continuous AED drug treatment in individuals with single or multiple calcified cysticercal lesions and epilepsy with no risk factors for seizure recurrence in resource-poor settings may outweigh the benefits of continuous AED therapy.

Additional remarks

Many factors may influence seizure recurrence in patients with epilepsy. For other considerations on managing epilepsy, see the WHO guidelines on epilepsy management.

EVIDENCE PROFILE: QUESTIONS 8 AND 9

8	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal cysts, which anthelmintics and AEDs are more beneficial or harmful than a placebo or control therapy?
Population	Individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable brain cysts
Intervention	Anthelmintic therapy (ALB or PZQ with corticosteroids) and/or AEDs (phenobarbital, phenytoin, carbamazepine or valproic acid)
Comparator	Placebo or control
Outcome	Seizure recurrence, adverse events

9	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal brain cysts, are higher doses and longer treatment with anthelmintics, anti-inflammatory agents and AEDs necessary for better clinical outcomes than standard neurocysticercosis treatment?
Population	Individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable brain cysts
Intervention	Higher doses and longer treatment with neurocysticercosis treatment (anthelmintics, anti-inflammatory agents, AEDs)
Comparator	Standard dose and duration of neurocysticercosis treatment (anthelmintics, anti-inflammatory agents, AEDs)
Outcome	Better clinical outcomes: faster resolution of neurological symptoms/signs, fewer episodes of seizure relapse or more frequent achievement of seizure-free status

Background

Many regions that are endemic for *T. solium* taeniasis and (neuro)cysticercosis are also endemic for HIV/AIDS *(51)*. Pathophysiological interactions exist for other coinfections of HIV such as HIV/AIDS and malaria, HIV/AIDS and tuberculosis and other helminths *(93)*. One area of interaction between neurocysticercosis and HIV/AIDS is in treatment, as development of an immune reconstitution inflammatory syndrome is possible when individuals with HIV/AIDS and asymptomatic neurocysticercosis start on highly active antiretroviral therapy, which can convert it to symptomatic neurocysticercosis *(94)*, and drug interactions may occur with AEDs in patients treated for seizures and antiretroviral medication *(95)*.

This systematic review was conducted to evaluate the literature on individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal brain cysts, particularly with regard to scaling up (higher doses, longer treatment) neurocysticercosis treatment (anthelmintics, anti-inflammatory agents, AEDs), whether it results in better clinical outcomes than standard neurocysticercosis treatment and which anthelmintic and AEDs produce benefit and/or harm when compared with a placebo or controls.

Inclusion and exclusion criteria

The search strategy and results are given in Annex 3 and section 2.3.2 (Fig. 3), respectively.

INCLUSION CRITERIA:	
Types of study:	Experimental and observational studies
Types of participant:	Individuals living with HIV/AIDS and neurocysticercosis
Types of intervention:	No restriction on treatment interventions
Types of outcome measure:	No restriction
Exclusion criteria:	We excluded individuals with neurocysticercosis but without HIV/AIDS, individuals with HIV/AIDS but without neurocysticercosis and individuals with neurocysticercosis coinfected with diseases other than HIV/AIDS.

Summary of findings

There is some suggestion that the clinical presentation of neurocysticercosis is different in people living with HIV/AIDS and in HIV-negative controls, such as higher percentages of symptomatic and multi-cystic disease. Because of the paucity of studies, however, no conclusion could be reached. Furthermore, no relevant studies were identified on the treatment of individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal cysts. Case reports and other documents were identified in a scoping review, and the results have been summarized in a publication in preparation.[2] Treatment and adverse outcomes in people living with HIV/AIDS and coinfected with neurocysticercosis are shown in tables A4.6.1 and A4.6.2. The findings are in line with those of another literature review on HIV/AIDS and neurocysticercosis coinfection *(96)*.

The available literature does not allow a conclusion on whether the standard of care for individuals only with viable parenchymal brain cysts and those with concomitant HIV/AIDS should differ. Drug interactions between antiretrovirals, anthelmintics and AEDs should be considered carefully. Further research is necessary to answer questions 8 and 9.

[2] Jewell P, Abraham A, Schmidt V, Buell KG, Bustos J, Garcia HH, et al. Neurocysticercosis and HIV/AIDS coinfection: a scoping review [in preparation].

Table A4.6.1. Case reports: treatment and outcomes of people living with HIV/AIDS and coinfected with neurocysticercosis

Ref.	Age (mean)	Sex	Country	Surgery	Anthelmintic, dose, duration (days)			Steroid, dose		Seizures, AED		Antiretro-viral therapy	Other therapy	Clinical outcome	Radiological outcome
97	49	M	Namibia	N	ALB	800 mg/ day	14	PRED	30 mg/ day	N	N	TDF, FTC, EFV	N	Favourable	Complete resolution
98	35	M	India	N	ALB	15 mg/ kg per day	28	PRED	NS	Y	NS	Y (NS)	N	Favourable	NS
98	40	M	India	N	ALB	15 mg/ kg per day	28	PRED	NS	Y	LEV	Y (NS)	N	Favourable, no further seizures	NS
99	22	F	Ecuador	N	ALB	800 mg/ day	30	DXM	8 mg/ day	N	PHE	ZDV, 3TC, ABC	N	Favourable	Improvement with calcification of cysts
100	45	M	Haiti	Laminec-tomy and epidural cyst removal	ALB	800 mg/ day	10	NS		N	N	ZDV, 3TC, ABC	N	Improved but persistent symptoms	Complete resolution
101	32	M	India	Xenon arc photocoag-ulation	N			N		N	N	ZDV	Anti-TB (NS)	Favourable	N/A
102	24	M	Burkina Faso	N	ALB	15 mg/ kg per day	14	DXM	8 mg/ day	Y	NS	NS	Anti-toxo (NS)	Favourable	Near-complete resolution
103	13	M	India	N	ALB	NS	14	Y (NS)	NS	Y	VAL, PHE	NS	N	Favourable	NS

104	39	F	Thailand	External ventricular drain	ALB	800 mg/ day	NS	PRED	100 mg/ day	N	N	N	N	Died	N/A
105, 106	26	F	DRC	N	PZQ	50 mg/ kg per day	NS	DXM	NS	Y	Y (NS)	N	AP	Favourable	Improved appearance
107	36	F	Brazil	N	ALB	15 mg/ kg per day	8	NS		Y	PHE	D4T, 3TC, EFV	PYR/ SLD	Favourable	NS
108	34	M	Burkina Faso	N	ALB	NS	NS	PRED	NS	Y	CBZ	NS	N	Favourable, no further seizures	NS
109	46	F	South Africa	Laminec- tomy and epidural cyst removal	ALB	15 mg/ kg per day	NS	DXM	8 mg/ day	N	N	NS	N	Persistent weakness	NS
110	27	F	Gabon	N	ALB	15 mg/ kg per day	NS	PRED	1 mg/ kg per day	Y	PHB	NS	N	Favourable	Complete resolution
111	24	M	India	N	PZQ	50 mg/ kg per day	NS	NS		N	N	Y (NS)	AMB	NS	NS
112	51	F	India	N	ALB	NS	NS	Y (NS)	NS	Y	Y (NS)	Y (NS)	Anti- toxo (NS)	Delayed clinical improvement	Persistent lesions
112	40	M	Honduras	N	N			N		Y	Y (NS)	Y (NS)	Anti- toxo (NS)	Favourable	NS
112	72	M	Peru	N	ALB	NS	NS	DXM	NS	N	N	N	N	Delayed clinical improvement	NS

113	36	F	Colombia	N	ALB	800 mg/ day	NS	DXM	16 mg/ day	N	N	ZDV, 3TC, LOPr	Anti-toxo (NS)	Died	N/A
114	27	F	Honduras	N	ALB	NS	NS	NS		Y	NS	Y (NS)	Anti-toxo (NS) GCV	Favourable, no further seizures	NS
94	35	M	multiple	Craniotomy and cyst excision	NS			NS		Y	NS	TDF, 3TC, EFV	N	Favourable	NS
115	29	M	Mexico	Craniotomy and cyst excision	ALB	15 mg/ kg per day	NS	NS		N	N	ZDV	N	Favourable	NS
115	41	F	Mexico	VP shunt	N			DXM	NS	N	N	NS	PYR, SXT	Favourable	NS
116	34	F	DRC	N	ALB	15 mg/ kg per day	15	DXM	6 mg/ day	Y	PHE, CBZ	TDF, FTC, ATV/r	N	Favourable	Complete resolution
117	40	M	Zimbabwe	N	ALB	NS	14	Y (NS)	NS	Y	N	NS	N	Slight improvement	NS
117	30	M	Zimbabwe	N	PZQ	NS	14	Y (NS)	NS	N	N	NS	N	No improvement	NS
117	36	M	Zimbabwe	N	PZQ	NS	NS	NS		Y	PHE	NS	N	Persistent seizures	NS
117	25	M	Zimbabwe	N	NS			NS		Y	NS	NS	N	Died	N/A
118	29	M	Mexico	N	N			NS		N	N	NS	AMB	Favourable	NS

3TC: lamivudine; ABC: abacavir; AED: antiepileptic drug; ALB: albendazole; AMB: amphotericin B; ATZ/r: atazanavir and ritonavir; CBZ: carbamazepine; DXM: dexamethasone; DRC: Democratic Republic of the Congo; EFV: efavirenz; FTC: emtricitabine; GCV: ganciclovir; LEV: levetiracetam; LOP/r: lopinovir and ritonavir; N: No/none; N/A: not applicable; NS: not specified or not known; PHB: phenobarbital; PHE: phenytoin; PRED: prednisolone; PYR: pyrimethamine; PZQ: praziquantel; SLD: sulfadiazine; SXT: trimethoprim sulfamethoxazole; TB: tuberculosis; TDF: tenofovir; VAL: sodium valproate; VP: ventriculoperitoneal; Y: Yes; ZDV: zidovudine

Table A4.6.2. Case reports: treatment, additional medications and adverse outcomes of people living with HIV/AIDS coinfected with neurocysticercosis

Treatment	Cases	Adjuvant steroid	Antiepileptic therapy	Antiretroviral therapy	Favourable outcome	Adverse outcomes
Albendazole	15/29 (52%)	13/15 (87%)	8/15 (53%)	9/15 (60%)	11/15 (73%)	1 (7%) died 3 (20%) delayed or slight clinical response
Praziquantel	4/29 (14%)	2/4 (50%)	2/4 (50%)	1/4 (25%)	2/4 (50%)	2 (50%) persistent or no improvement in symptoms
Surgery plus albendazole	4/29 (15%)	0	0	0	1/4 (25%)	1 (25%) died 2 (50%) persistent symptoms
Surgery alone	3/29 (10%)	N/A	0	2/3 (67%)	3/3 (100%)	None reported
None or not specified	3/29 (10%)	N/A	1/3 (33%)	1/3 (33%)	2/3 (67%)	1 (33%) died

N/A, not applicable

Quality assessment

Because only case reports were identified, GRADE tables could not be made for PICO questions 8 and 9.

Evidence for recommendations

8	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal brain cysts, which anthelmintics and AEDs are more beneficial or harmful than a placebo or control therapy?
9	In individuals living with HIV/AIDS and symptomatic neurocysticercosis with viable parenchymal brain cysts, are higher doses and longer treatment with anthelmintics, anti-inflammatory agents and AEDs necessary for better clinical outcomes than standard neurocysticercosis treatment?
Factor	Explanation
Narrative summary of the evidence base	Only case reports were identified.

Summary of the quality of evidence	The quality of evidence was graded as very low.
Values and preferences including any variability and human rights issues	From the perspective of people with epilepsy or seizures: the factors in favour of anthelmintic treatment of symptomatic individuals with neurocysticercosis and HIV/AIDS are the: importance of the intervention for better seizure control importance of the intervention for better cyst resolution importance of the outcomes for better social functioning, decrease in stigma/discrimination the factors against anthelmintic treatment of symptomatic individuals with neurocysticercosis and HIV/AIDS are the: importance of adverse events due to the intervention importance of economic loss due to hospitalization for interventions importance of lack of availability of neuroimaging facilities
Costs and resource use and any other relevant feasibility issues	Availability and price of anthelmintic therapy (on the WHO List of Essential Medicines) Access to and costs of neuroimaging, which is standard practice before initiation of anthelmintic medication with corticosteroids Training of clinical personnel

Final recommendation(s)

Patients with neurocysticercosis who are coinfected with HIV should be treated according to the guidelines for treating patients with neurocysticercosis without HIV/AIDS.

Clinical and regional consideration(s)

Few data are available on individuals coinfected with neurocysticercosis and HIV/AIDS.

There are no data on potential interactions of antiretroviral medicines and anthelmintic, anti-inflammatory and AEDs in individuals coinfected with neurocysticercosis and HIV.

There are no data on the potential association between immune reconstitution inflammatory syndrome and neurocysticercosis in individuals with neurocysticercosis who begin antiretroviral therapy for HIV/AIDS. Caution should therefore be used when initiating therapy in individuals coinfected with neurocysticercosis and HIV. Treatment of individuals with HIV/AIDS should follow WHO guidelines on HIV/AIDS.

AED treatment for epilepsy in individuals coinfected with neurocysticercosis and HIV should follow WHO guidelines for patients infected with HIV and epilepsy *(119)*.

Anthelmintic treatment of individuals coinfected with neurocysticercosis and HIV should be provided according to the literature on patients infected with HIV and neglected tropical diseases.

Research gap(s)

What is the optimal drug(s), dose, duration and combination of anthelmintic therapy for individuals with neurocysticercosis and HIV/AIDS?

What is the effect of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) on seizure severity or frequency, long-term seizure recurrence and reduced duration of AED therapy in individuals with neurocysticercosis and HIV/AIDS?

What are the adverse events of anthelmintic therapy in combination with anti-inflammatory therapy (corticosteroids) in individuals with neurocysticercosis and HIV/AIDS?

What is the optimal drug(s), dose and duration of anti-inflammatory therapy (corticosteroids) in individuals with neurocysticercosis and HIV/AIDS?

What is the effect of anti-inflammatory therapy (corticosteroids) alone on seizure severity or frequency, long-term seizure recurrence and reduced duration of AED therapy in individuals with neurocysticercosis and HIV/AIDS?

What are the adverse events of anti-inflammatory therapy (corticosteroids) alone in individuals with neurocysticercosis and HIV/AIDS?

What is the optimal drug(s), dose and duration of AED therapy in individuals in individuals with neurocysticercosis and HIV/AIDS?

What are the side-effects of AED therapy in individuals with neurocysticercosis and HIV/AIDS?

Does immune reconstitution inflammatory syndrome occur in individuals with neurocysticercosis who begin antiretroviral therapy for HIV/AIDS?

If the answer to the above question is positive, what are the clinical characteristics of immune reconstitution inflammatory syndrome in individuals with neurocysticercosis and HIV/AIDS?

Strength of recommendation(s)

Conditional – The recommendation was considered conditional because of the lack of evidence for treatment of individuals with neurocysticercosis and HIV/AIDS. The guidelines listed under "clinical considerations" should be followed.

Additional remarks

Well-designed clinical trials of individuals with neurocysticercosis and HIV/AIDS should be conducted urgently to answer the above research questions.

References to Annex 4

1. Del Brutto OH. Neurocysticercosis. Handb Clin Neurol. 2014;121:1445–9.
2. Roman G, Sotelo J, Del Brutto O, Flisser A, Dumas M, Wadia N et al. A proposal to declare neurocysticercosis an international reportable disease. Bull World Health Organ. 2000;78(3):399–406.
3. Relationship between epilepsy and tropical diseases. Commission on Tropical Diseases of the International League Against Epilepsy. Epilepsia. 1994;35(1):89–93.
4. Escobar A. The pathology of neurocysticercosis. In: Palacios E, Rodriguez-Carbajal J, Taveras JM, editors. Cysticercosis of the central nervous system. Springfield (IL): Charles C. Thomas; 1983:27.
5. Garcia HH, Del Brutto OH. Imaging findings in neurocysticercosis. Acta Trop. 2003;87(1):71–8.
6. Aguilar Rebolledo F. Perfil de la neurocisticercosis en niños mexicanos [Profile of neurocisticercosis in Mexican children]. Cirug Cirujan. 1998;66(3):89–99.
7. Barloon TJ, Yuh WT, Chiang FL, Kao SC, Sato Y, Mehringer M. Lesions involving the fourth ventricle evaluated by CT and MR: a comparative study. Magn Reson Imaging. 1989;7(6):635–42.
8. Citow JS, Johnson JP, McBride DQ, Ammirati M. Imaging features and surgery-related outcomes in intraventricular neurocysticercosis. Neurosurg Focus. 2002;12(6):e6.
9. Del Brutto OH. Neurocysticercosis in children: clinical and radiological analysis and prognostic factors in 54 patients. Rev Neurol. 1997;25(147):1681–4.
10. Del Brutto OH, Salgado P, Lama J, Del Brutto VJ, Campos X, Zambrano M et al. Calcified neurocysticercosis associates with hippocampal atrophy: a population-based study. Am J Trop Med Hyg. 2015;92(1):64–8.
11. Garg RK, Karak B, Mohan Kar A. Neuroimaging abnormalities in Indian patients with uncontrolled partial seizures. Seizure. 1998;7(6):497–500.
12. Gongora-Rivera F, Soto-Hernandez JL, Gonzalez Esquivel D, Cook HJ, Marquez-Caraveo C, Hernandez Davila R et al. Albendazole trial at 15 or 30 mg/kg/day for subarachnoid and intraventricular cysticercosis. Neurology. 2006;66(3):436–8.
13. Govindappa SS, Narayanan JP, Krishnamoorthy VM, Shastry CH, Balasubramaniam A, Krishna SS. Improved detection of intraventricular cysticercal cysts with the use of three-dimensional constructive interference in steady state MR sequences. Am J Neuroradiol. 2000;21(4):679–84.
14. Martinez HR, Rangel-Guerra R, Elizondo G, Gonzalez J, Todd LE, Ancer J et al. MR imaging in neurocysticercosis: a study of 56 cases. Am J Neuroradiol. 1989;10(5):1011–9.
15. Morgado C, Gomes LB, de Campos JG. Neurocysticercosis. An imaging analysis of 35 cases. Acta Med Port. 1994;7(5):269–75.
16. Puri V, Gupta RK. Magnetic resonance imaging evaluation of focal computed tomography abnormality in epilepsy. Epilepsia. 1991;32(4):460–6.
17. Rajshekhar V, Chandy MJ. Comparative study of CT and MRI in patients with seizures and a solitary cerebral cysticercus granuloma. Neuroradiology. 1996;38(6):542–6.
18. Roy B, Verma S, Awasthi R, Rathore RK, Venkatesan R, Yoganathan SA et al. Correlation of phase values with CT Hounsfield and R2* values in calcified neurocysticercosis. J Magn Reson Imaging. 2011;34(5):1060–4.
19. Souza A, Nalini A, Srikanth SG. Solitary cerebral parenchymal cysticercosis: a prospective comparative study with computed tomography and magnetic resonance imaging. Neurol India. 2013;61(6):639–43.

20. Suss RA, Maravilla KR, Thompson J. MR imaging of intracranial cysticercosis: comparison with CT and anatomopathologic features. Am J Neuroradiol. 1986;7(2):235–42.

21. Teitelbaum GP, Otto RJ, Lin M, Watanabe AT, Stull MA, Manz HJ et al. MR imaging of neurocysticercosis. Am J Roentgenol. 1989;153(4):857–66.

22. Zee CS, Segall HD, Boswell W, Ahmadi J, Nelson M, Colletti P. MR imaging of neurocysticercosis. J Comput Assist Tomogr. 1988;12(6):927–34.

23. Puri V, Gupta RK. Magnetic resonance imaging evaluation of focal computed tomography abnormality in epilepsy. Epilepsia. 1991;32(4):460–6.

24. Morgado C, Gomes LB, de Campos JG. Neurocysticercosis. An imaging analysis of 35 cases. Acta Med Port. 1994;7(5):269–75.

25. Zee CS, Segall HD, Boswell W, Ahmadi J, Nelson M, Colletti P. MR imaging of neurocysticercosis. J Comput Assist Tomogr. 1988;12(6):927–34.

26. Teitelbaum GP, Otto RJ, Lin M, Watanabe AT, Stull MA, Manz HJ et al. MR imaging of neurocysticercosis. Am J Roentgenol. 1989;153(4):857–66.

27. Garcia HH, Gonzalez AE, Evans CA, Gilman RH, Cysticercosis Working Group in Peru. *Taenia solium* cysticercosis. Lancet. 2003;362(9383):547–56.

28. Tsang V, Wilson M. *Taenia solium* cysticercosis: an under-recognized but serious public health problem. Parasitol Today. 1995;11(3):124–6.

29. Nash TE, Neva FA. Recent advances in the diagnosis and treatment of cerebral cysticercosis. N Engl J Med. 1984;311(23):1492–6.

30. Robles C. Medical treatment of cerebral cysticercosis. Gac Med Mex. 1981;117(9):355–63.

31. Botero D, Castano S. Treatment of cysticercosis with praziquantel in Colombia. Am J Trop Med Hyg. 1982;31(4):811–21.

32. Sotelo J, Escobedo F, Rodriguez-Carbajal J, Torres B, Rubio-Donnadieu F. Therapy of parenchymal brain cysticercosis with praziquantel. N Engl J Med. 1984;310(16):1001–7.

33. Romo ML, Wyka K, Carpio A, Leslie D, Andrews H, Bagiella E et al. The effect of albendazole treatment on seizure outcomes in patients with symptomatic neurocysticercosis. Trans R Soc Trop Med Hyg. 2015;109(11):738–46.

34. Alarcón F, Duenas G, Diaz M, Cevallos N. Short course of albendazole therapy for neurocysticercosis: a prospective randomized trial comparing three days, eight days and the control group without albendazole. Rev Ecuator Neurol. 2001;10:1–6.

35. Carpio A, Kelvin EA, Bagiella E, Leslie D, Leon P, Andrews H et al. Effects of albendazole treatment on neurocysticercosis: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2008;79(9):1050–5.

36. Das K, Mondal GP, Banerjee M, Mukherjee BB, Singh OP. Role of antiparasitic therapy for seizures and resolution of lesions in neurocysticercosis patients: an 8 year randomised study. J Clin Neurosci. 2007;14(12):1172–7.

37. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med. 2004;350(3):249–58.

38. Alarcon F, Escalante L, Duenas G, Montalvo M, Roman M. Neurocysticercosis. Short course of treatment with albendazole. Arch Neurol. 1989;46(11):1231–6.

39. Carpio A, Santillan F, Leon P, Flores C, Hauser WA. Is the course of neurocysticercosis modified by treatment with antihelminthic agents? Arch Intern Med. 1995;155(18):1982–8.

40. Padma MV, Behari M, Misra NK, Ahuja GK. Albendazole in neurocysticercosis. Natl Med J

India. 1995;8(6):255–8.

41. Sotelo J, Escobedo F, Penagos P. Albendazole vs praziquantel for therapy for neurocysticercosis. A controlled trial. Arch Neurol. 1988;45(5):532–4.

42. Cuello-Garcia CA, Roldan-Benitez YM, Perez-Gaxiola G, Villarreal-Careaga J. Corticosteroids for neurocysticercosis: a systematic review and meta-analysis of randomized controlled trials. Int J Infect Dis. 2013;17(8):e583–92.

43. Garcia HH, Gonzales I, Lescano AG, Bustos JA, Pretell EJ, Saavedra H et al. Enhanced steroid dosing reduces seizures during antiparasitic treatment for cysticercosis and early after. Epilepsia. 2014;55(9):1452–9.

44. Singh MK, Garg RK, Nath G, Verma DN, Misra S. Single small enhancing computed tomographic (CT) lesions in Indian patients with new-onset seizures. A prospective follow-up in 75 patients. Seizure. 2001;10(8):573–8.

45. Chandy MJ, Rajshekhar V, Ghosh S, Prakash S, Joseph T, Abraham J et al. Single small enhancing CT lesions in Indian patients with epilepsy: clinical, radiological and pathological considerations. J Neurol Neurosurg Psychiatry. 1991;54(8):702–5.

46. Chandy MJ, Rajshekhar V, Prakash S, Ghosh S, Joseph T, Abraham J et al. Cysticercosis causing single, small CT lesions in Indian patients with seizures. Lancet. 1989;1(8634):390–1.

47. Rajshekhar V, Jeyaseelan L. Seizure outcome in patients with a solitary cerebral cysticercus granuloma. Neurology. 2004;62(12):2236–40.

48. Zhao BC, Jiang HY, Ma WY, Jin DD, Li HM, Lu H et al. Albendazole and corticosteroids for the treatment of solitary cysticercus granuloma: a network meta-analysis. PLoS Negl Trop Dis. 2016;10(2):e0004418.

49. Otte WM, Singla M, Sander JW, Singh G. Drug therapy for solitary cysticercus granuloma: a systematic review and meta-analysis. Neurology. 2013;80(2):152–62.

50. Padma MV, Behari M, Misra NK, Ahuja GK. Albendazole in single CT ring lesions in epilepsy. Neurology. 1994;44(7):1344–6.

51. Gogia S, Talukdar B, Choudhury V, Arora BS. Neurocysticercosis in children: clinical findings and response to albendazole therapy in a randomized, double-blind, placebo-controlled trial in newly diagnosed cases. Trans R Soc Trop Med Hyg. 2003;97(4):416–21.

52. Baranwal AK, Singhi PD, Khandelwal N, Singhi SC. Albendazole therapy in children with focal seizures and single small enhancing computerized tomographic lesions: a randomized, placebo-controlled, double blind trial. Pediatr Infect Dis J. 1998;17(8):696–700.

53. Kalra V, Dua T, Kumar V. Efficacy of albendazole and short-course dexamethasone treatment in children with 1 or 2 ring-enhancing lesions of neurocysticercosis: a randomized controlled trial. J Pediatr. 2003;143(1):111–4.

54. Mall RK, Agarwal A, Garg RK, Kar AM, Shukla R. Short course of prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures. Epilepsia. 2003;44(11):1397–1401.

55. Garg RK, Potluri N, Kar AM, Singh MK, Shukla R, Agrawal A et al. Short course of prednisolone in patients with solitary cysticercus granuloma: a double blind placebo controlled study. J Infect. 2006;53(1):65–9.

56. Singhi P, Jain V, Khandelwal N. Corticosteroids versus albendazole for treatment of single small enhancing computed tomographic lesions in children with neurocysticercosis. J Child Neurol. 2004;19(5):323–7.

57. Prakash S, Garg RK, Kar AM, Shukla R, Agarwal A, Verma R et al. Intravenous methyl prednisolone in patients with solitary cysticercus granuloma: a random evaluation. Seizure. 2006;15(5):328–32.

58. Sharma SR, Agarwal A, Kar A, Shukla R, Garg RK. Evaluation of role of steroid alone and with albendazole in patients of epilepsy with single-small enhancing computerized tomography lesions. Ann Indian Acad Neurol. 2007;10(1):39–43.

59. Kishore D, Misra S. Short course of oral prednisolone on disappearance of lesion and seizure recurrence in patients of solitary cysticercal granuloma with single small enhancing CT lesion: an open label randomized prospective study. J Assoc Physicians India. 2007;55:419–24.

60. Thussu A, Chattopadhyay A, Sawhney IM, Khandelwal N. Albendazole therapy for single small enhancing CT lesions (SSECTL) in the brain in epilepsy. J Neurol Neurosurg Psychiatry. 2008;79(3):272–5.

61. de Souza A, Thennarasu K, Yeshraj G, Kovoor JM, Nalini A. Randomized controlled trial of albendazole in new onset epilepsy and MRI confirmed solitary cerebral cysticercal lesion: effect on long-term seizure outcome. J Neurol Sci. 2009;276(1–2):108–14.

62. Singla M, Prabhakar S, Modi M, Medhi B, Khandelwal N, Lal V. Short-course of prednisolone in solitary cysticercus granuloma: a randomized, double-blind, placebo-controlled trial. Epilepsia. 2011;52(10):1914–7.

63. Chaurasia RN, Garg RK, Agarwall A, Kohli N, Verma R, Singh MK et al. Three day albendazole therapy in patients with a solitary cysticercus granuloma: a randomized double blind placebo controlled study. Southeast Asian J Trop Med Public Health. 2010;41(3):517–25.

64. Pretell EJ, Garcia HH, Custodio N, Padilla C, Alvarado M, Gilman RH et al. Short regimen of praziquantel in the treatment of single brain enhancing lesions. Clin Neurol Neurosurg. 2000;102(4):215–8.

65. de Souza A, Nalini A, Kovoor JM, Yeshraj G, Siddalingaiah HS, Thennarasu K. Perilesional gliosis around solitary cerebral parenchymal cysticerci and long-term seizure outcome: a prospective study assessing serial magnetization transfer imaging. Epilepsia. 2011;52(10):1918–27.

66. Khurana N, Garg RK, Verma R, Malhotra HS, Singh MK, Shukla R. Three-day versus 15-day course of albendazole therapy in solitary cysticercus granuloma: an open label randomized trial. J Neurol Sci. 2012;316(1–2):36–41.

67. de Souza A, Nalini A, Saini J, Thennarasu K. T2 relaxometry helps prognosticate seizure outcome in patients with solitary cerebral cysticercosis. J Neurol Sci. 2017;376:1–6.

68. Abraham A, Bustos JA, Carabin H, de Meijere R, Sahu PS, Rajshekhar V et al. The effectiveness of anti-inflammatory and anti-seizure medication for individuals with single enhancing lesion neurocysticercosis: a meta-analysis and expert group-based consensus recommendations. PLoS Negl Trop Dis. 2021;15(3):e0009193.

69. Kalra V, Mittal R. Duration of antiepileptic drug (AED) therapy. Indian J Pediatr. 1998;65(5):772-5. doi: 10.1007/BF02731068. PMID: 10773939.

70. Sharma M, Singh T, Mathew A. Antiepileptic drugs for seizure control in people with neurocysticercosis. Cochrane Database Syst Rev. 2015;(10):CD009027.

71. Thussu A, Arora A, Prabhakar S, Lal V, Sawhney IM. Acute symptomatic seizures due to single CT lesions: how long to treat with antiepileptic drugs? Neurol India. 2002;50(2):141–4.

72. Gupta M, Agarwal P, Khwaja GA, Chowdhury D, Sharma B, Bansal J et al. Randomized prospective study of outcome of short term antiepileptic treatment in small single enhancing CT lesion in brain. Neurol India. 2002;50(2):145–7.

73. Singhi PD, Dinakaran J, Khandelwal N, Singhi SC. One vs two years of anti-epileptic therapy in children with single small enhancing CT lesions. J Trop Pediatr. 2003;49(5):274–8.

74. Verma A, Misra S. Outcome of short-term antiepileptic treatment in patients with solitary cerebral cysticercus granuloma. Acta Neurol Scand. 2006;113(3):174–7.

75. Nash TE, Pretell EJ, Lescano AG, Bustos JA, Gilman RH, Gonzalez AE et al. Perilesional brain oedema and seizure activity in patients with calcified neurocysticercosis: a prospective cohort and nested case-control study. Lancet Neurol. 2008;7(12):1099–105.

76. Del Brutto OH. Prognostic factors for seizure recurrence after withdrawal of antiepileptic drugs in patients with neurocysticercosis. Neurology. 1994;44(9):1706–9.

77. Commission on Tropical Diseases of the International League Against Epilepsy. Relationship between epilepsy and tropical diseases. Epilepsia. 1994;35(1):89–93.

78. Birbeck GL. Epilepsy care in developing countries: part I of II. Epilepsy Curr. 2010;10(4):75–9.

79. Sánchez AL, Lindbäck J, Schantz PM, Sone M, Sakai H, Medina MT et al. A population-based, case–control study of *Taenia solium* taeniasis and cysticercosis. Ann Trop Med Parasitol. 1999;93(3):247–58.

80. Fleury A, Gomez T, Alvarez I, Meza D, Huerta M, Chavarria A et al. High prevalence of calcified silent neurocysticercosis in a rural village of Mexico. Neuroepidemiology. 2003;22(2):139–45.

81. Moyano LM, O'Neal SE, Ayvar V, Gonzalvez G, Gamboa R, Vilchez P et al. High prevalence of asymptomatic neurocysticercosis in an endemic rural community in Peru. PLoS Negl Trop Dis. 2016;10(12):e0005130.

82. Del Brutto OH, Issa NP, Salgado P, Del Brutto VJ, Zambrano M, Lama J et al. The association between neurocysticercosis and hippocampal atrophy is related to age. Am J Trop Med Hyg. 2017;96(1):243–8.

83. Garcia HH, Gilman R, Martinez M, Tsang VC, Pilcher JB, Herrera G et al. Cysticercosis as a major cause of epilepsy in Peru. The Cysticercosis Working Group in Peru. Lancet. 1993;341(8839):197–200.

84. Bruno E, Bartoloni A, Zammarchi L, Strohmeyer M, Bartalesi F, Bustos JA et al. Epilepsy and neurocysticercosis in Latin America: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2013;7(10):e2480.

85. Debacq G, Moyano LM, Garcia HH, Boumediene F, Marin B, Ngoungou EB et al. Systematic review and meta-analysis estimating association of cysticercosis and neurocysticercosis with epilepsy. PLoS Negl Trop Dis. 2017;11(3):e0005153.

86. Hussain J, Srinivasan S, Serane VT, Mahadevan S, Elangovan S, Bhuvaneswari V. Cranial computed tomography in partial motor seizures. Indian J Pediatr. 2004;71(7):641–4.

87. Nash TE, Del Brutto OH, Butman JA, Corona T, Delgado-Escueta A, Duron RM et al. Calcific neurocysticercosis and epileptogenesis. Neurology. 2004;62(11):1934–8.

88. Del Brutto OH, Campos X. Discontinuation of antiepileptic drugs in patients with calcified neurocysticercosis. J Epilepsy. 1996;9(4):231–3.

89. Narayana RV, Pati R. Do calcified lesions require longer duration of treatment? Epilepsia. 2011;52(Suppl. 6):p065.

90. mhGAP intervention guide, version 2.0 for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization; 2019 (https://www.who.int/publications/i/item/mhgap-intervention-guide---version-2.0, accessed 23 March 2021).

91. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.

92. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.

93. Landscape analysis: management of neurocysticercosis with an emphasis on low- and

middle-income countries. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/152896/WHO_HTM_NTD_NZD_2015.05_eng.pdf?sequence, accessed May 2021).

94. Serpa JA, Moran A, Goodman JC, Giordano TP, White AC Jr. Neurocysticercosis in the HIV era: a case report and review of the literature. Am J Trop Med Hyg. 2007;77(1):113–7.

95. Bhigjee AI, Rosemberg S. Optimizing therapy of seizures in patients with HIV and cysticercosis. Neurology. 2006;67(12 Suppl 4):S19–22.

96. Herrera Vazquez O, Romo ML, Fleury A. Neurocysticercosis and HIV Infection: what can we learn from the published literature? Arq Neuropsiquiatr. 2019;77(5):357–65.

97. Agaba E, Modi D, Gunduz O, Modi Z. Subcutaneous nodules of cysticercosis as a sign of asymptomatic neurocysticercosis in an HIV positive patient. Rev Soc Bras Med Trop. 2018;51(6):861–3.

98. Anand KS, Wadhwa A, Garg J, Mahajan RK. HIV-associated neurocysticercosis. J Int Assoc Provid AIDS Care. 2015;14(2):120–2.

99. Chianura L, Sberna M, Moioli C, Villa MR, Orcese C, Causarano R. Neurocysticercosis and human immunodeficiency virus infection: a case report. J Travel Med. 2006;13(6):376–80.

100. Delobel P, Signate A, El Guedj M, Couppie P, Gueye M, Smadja D et al. Unusual form of neurocysticercosis associated with HIV infection. Eur J Neurol. 2004;11(1):55–8.

101. George AE, Biswas J, Agarwal R, Kumarasamy N, Solomon S. Subretinal cysticercosis in a patient with AIDS: treatment with xenon arc photocoagulation. Retina. 1999;19(5):467–8.

102. Giordani MT, Tamarozzi F, Cattaneo F, Brunetti E. Three cases of imported neurocysticercosis in northern Italy. J Travel Med. 2014;21(1):17–23.

103. Gupta V, Yadav TP. "Starry sky"-appearing neurocysticercosis in paediatric HIV infection. J Indian Acad Clin Med. 2012;13(4):316–8.

104. Itani MM, Jørgensen GM. Cerebral cysticerci is a rare cause of hydrocephalus. Ugeskr Laeg. 2013;175(23):1651–2.

105. Jung A, Thaker H, Ming A. Casualties of conflict: a case report of neurocysticercosis, reactivation of toxoplasmosis in an HIV positive pregnant patient (P2542). Eur J Neurol. 2008;15(Suppl. 3):342.

106. Lillie P, Parsonage M, Barlow G, Thaker H. Neurocysticercosis with communicating hydrocephalus in an HIV-positive patient (P105). HIV Med. 2006;7(Suppl. 1):27.

107. Martins JCM, Cruzeiro MM, Pires LA. Neurotoxoplasmosis and neurocysticercosis in patient with AIDS – case report. Rev Neuroci. 2015;23(03):443–50.

108. Millogo A. Epilepsy revealing neurocysticercosis in an HIV positive patient with subcutaneous nodules. N Afr Middle East Epilepsy J. 2013;2(1):8.

109. Motsepe T, Ackermann D. Spinal and vertebral neurocysticercosis in an HIV-positive female patient. South Afr J Epidemiol Infect. 2012;27(3):133–6.

110. Okome-Nkoumou MM, Ondounda M, Dzeing-Ella A, Mounguengui D, Madjinou MI, Clevenbergh P et al. Epileptiform seizures revealing neurocysticercosis: report of two clinical cases in Libreville, Gabon. Trop Doct. 2010;40(4):235–7.

111. Pandey K, Sinha PK, Das VR, Sur D, Kumar N, Bhattacharya SK. Neurocysticercosis in a patient with visceral leishmaniasis co-infected with HIV: a case report. Infect Dis Clin Pract. 2005;13(3):144–5.

112. Prasad S, MacGregor RR, Tebas P, Rodriguez LB, Bustos JA, White AC Jr. Management of potential neurocysticercosis in patients with HIV infection. Clin Infect Dis. 2006;42(4):e30–4.

113. Ramos JM, Masia M, Padilla S, Bernal E, Martin-Hidalgo A, Gutiérrez F. Fatal infection due to larval cysts of cestodes (neurocysticercosis and hydatid disease) in human immunodeficiency virus (HIV) infected patients in Spain: report of two cases. Scand J Infect Dis. 2007;39(8):719–23.

114. Ruziev SR, Moll CL, Engel LS. "Treated the horse but forgot the zebra": a case of neurocysticercosis. J Invest Med. 2010;58(2):407.

115. Soto Hernandez JL, Ostrosky Zeichner L, Tavera G, Gomez Avina A. Neurocysticercosis and HIV infection: report of two cases and review. Surg Neurol. 1996;45(1):57–61.

116. Taha H, Das S. Cerebral mass in HIV infection. BMJ. 2013;347:f6314.

117. Thornton CA, Houston S, Latif AS. Neurocysticercosis and human immunodeficiency virus infection. A possible association. Arch Neurol. 1992;49(9):963–5.

118. White AC Jr, Dakik H, Diaz P. Asymptomatic neurocysticercosis in a patient with AIDS and cryptococcal meningitis. Am J Med. 1995;99(1):101–2.

119. Anti-epileptic medications for adults and children with HIV. Geneva: World Health Organization; 2015 (https://www.who.int/mental_health/mhgap/evidence/epilepsy/q14/en/, accessed 22 June 2020).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