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REVIEW

Neurocysticercosis control for primary epilepsy prevention: a systematic review

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ABSTRACT

Neurocysticercosis (NCC) is a leading cause of preventable epilepsy in lower- and upper-middle-income countries (LMICs/UMICs). NCC is a human-to-human transmitted disease caused by ingestion of *Taenia solium* eggs from a *Taenia* carrier. *T. solium* infection control is the key to reduce NCC incidence. This systematic review aims to identify *T. solium* control programs that can provide frameworks for endemic areas to prevent NCC-related epilepsy. A systematic search was conducted in PubMed/Medline, Embase, Web of Science, and Cochrane Library databases in March 2021. After title and abstract review, full texts were screened for qualitative analysis. Additional articles were identified via citation search. Of 1322 total results, 34 unique studies were included. Six major intervention types were identified: national policy (8.8%), community sanitation improvement (8.8%), health education (8.8%), mass drug administration (29.4%), pig vaccination and treatment (32.4%), and combined human and pig treatment (11.8%). Overall, 28 (82.4%) studies reported decreased cysticercosis prevalence following the intervention. Only health education and combined human and pig treatment were effective in all selected studies. NCC causes preventable epilepsy in LMICs/UMICs and its incidence can be reduced through *T. solium* control. Most interventions that disrupt the *T. solium* transmission cycle are effective. Long-term sustained results require comprehensive programs, ongoing surveillance, and collaborative effort among multisectoral agencies.

KEYWORDS
Neurocysticercosis; infectious disease; epilepsy; global health; global neurosurgery

Introduction

Epilepsy affects 50–70 million people worldwide, with 2.56–8.30 million newly diagnosed cases each year [1]. Estimates of years lived with disability secondary to untreated and uncontrolled epilepsy are disproportionally higher in low- and middle-income countries (LMICs), where 80% of epilepsy-related deaths occur [2]. Etiologies of epilepsy in LMICs are commonly due to birth-related injuries, infections, traumatic brain injuries, and strokes [3]. Further, barriers in diagnosis and treatment of epilepsy in LMICs lead to a higher population with untreated diseases [4]. Management of epilepsy in LMICs is challenging and barriers to correct diagnosis of epilepsy has led to a larger number of untreated individuals [5]. Adequate seizure prevention often requires daily medications that are sometimes hard to find and inconsistently available in LMICs. Insufficient primary care infrastructure makes adherence to these antiseizure medications even more difficult [4]. For medically refractory epilepsy requiring surgical intervention, inadequate resources for neurosurgical and intensive care access further contribute to treatment gaps [6]. People with epilepsy frequently face social stigma, loss of work productivity, and compromised human rights [7]. Given the significant medical and economic sequalae of epilepsy, the need for prevention of this disease is paramount. The World Health Organization (WHO) endorsed action plans for epilepsy prevention in the 68 World Health Assembly (WHA 68.20) resolution and the road map for neglected tropical diseases [8,9]. Given the challenges of correct diagnosis and treatment of epilepsy in LMICs, to reduce the burden of this prevalent chronic 'silent' disease, a major public health aim has become the primary prevention of intracranial pathologies that result in seizures disorders.

Neurocysticercosis (NCC) is the infection of the central nervous system and meninges by the larval stage of the pork tapeworm, *Taenia solium* and is arguably the most important preventable cause of seizures

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around the world. Within endemic areas, it is estimated that 34% of seizure disorders are attributed to NCC [3]. NCC is caused by *T. solium* cystic larva entering the central nervous system (CNS) after a human host ingests *T. solium* eggs in fecal comtamination. The lifecycle of *T. solium* requires a human as a definite host that can house the adult tapeworm and the larval form and the pig as an intermediated host that can only house the larvae [10]. Humans ingest *T. solium* cysts from contaminated improperly cooked pork which develops into an adult tapeworm in the human intestinal wall. The tapeworm eggs enter the environment when human carriers defecate and in places lacking appropriate sanitation, both pigs and humans may access and ingest these contaminated stools thereby becoming infected with tapeworm eggs [11]. Free-range pigs that scavenge human feces ingest *T. solium* eggs, which develop into larvae that cross the intestinal mucosa into the bloodstream resulting in infection of the intermediate host and development of porcine cysticercosis [12]. Substandard meat-inspection at pig slaughterhouse allows pork infected by *T. solium* to enter human diet, particularly affecting cultures that consume pork [13]. Humans exposed to tapeworm eggs in human feces also can develop cysticercosis. Development of human cysticercosis often depends on close contact with a human tapeworm carrier and does not involve ingestion of infected pork. Once eggs are ingested, they hatch and cross intestinal mucosa and spread by the blood stream to tissues including the CNS [11]. Humans with *T. solium* infection often remain clinically silent for at least one year without immediate inflammatory responses [14,15]. Cysts can remain viable for years then eventually begin to degenerate. The most common presenting symptom of NCC is seizure due to cyst degeneration years after the initial infection and it has been found that recurrent seizures occur in about 80% of symptomatic cases of NCC [12]. To make the definitive diagnosis, advanced imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) is necessary. These modalities are often lacking or inaccessible in countries where *T. solium* is considered endemic. Treatment is largely dependent on anthelmintics, such as praziquantel and albendazole, or surgical resection [12].

T. solium infection predominantly affects countries with low economic development [16]. Lack of health education, poor sanitary control, and financial incentive of pig raising farmers are contributing factors to high rates of cysticercosis [17]. In high-income countries (HICs), the low incidence of human cysticercosis is attributed to mandatory national policies and public health surveillance, with most NCC cases found in immigrants from endemic areas in UMICs/LMICs [18,19]. In many LMICs, however, implementation of large-scale control programs is difficult due to country-specific contexts, differential resources, and diverse cultural beliefs [20]. To date, no systematic review has been conducted to evaluate the effectiveness of currently available cysticercosis control programs. By systematically identifying and evaluating different studied approaches to cysticercosis control, this review aims to highlight the programs found to be most successful at reducing incidence/prevalence of *T. solium* infection so that future LMIC policymakers can emulate them in order to reduce cysticercosis prevalence and ultimately reduce the incidence of NCC-related epilepsy.

Methods

A systematic review was conducted using PubMed/Medline, Embase, Cochrane library, and Web of Science databases in accordance with the PRISMA guideline [21]. Articles published in or translated to English from January 1990 to March 2021 were included. The search string used keywords associated with PICO (Population, Intervention, Comparison, Outcome) structure shown in Table 1. The search included populations at risk of *T. solium* infection, control measure interventions to reduce cysticercosis, and primary outcome of prevalence of human or porcine cysticercosis.

After completing the search on 26 March 2021, duplicates were removed, and remaining articles were screened based on titles and abstracts. During initial screening, articles were excluded if the wrong population or wrong intervention was reported. Full texts of selected publications were then retrieved for in-depth review. Additional records were identified

Table 1. Summary of search terms.

Database	Search Terms
PubMed/Medline	((((((neurocysticercosis) OR (cysticercosis)) OR (taeniasis)) OR ('taenia solium')) OR (cestodiasis)) AND ((((prevention) OR (eradication)) OR (elimination)) AND ((((program) OR (policy)) OR (regulation)) OR (intervention)))) AND (((((((incidence) OR (prevalence)) OR (burden)) OR (seizure)) OR (epilepsy)) OR (morbidity)) OR (mortality))
Embase	#1 neurocysticercosis OR cysticercosis OR taeniasis OR 'taenia solium' OR cestodiasis #2 prevention OR eradication OR elimination #3 program OR policy OR regulation OR intervention #4 incidence OR prevalence OR burden OR seizure OR epilepsy OR morbidity OR mortality #5 #1 AND #2 AND #3 AND #4
Cochrane Library	(Neurocysticercosis) OR (cysticercosis) OR (taeniasis) OR ('taenia solium') OR (cestodiasis)" (Word variations have been searched)
Web of Science	#1 ALL FIELDS: (neurocysticercosis) OR ALL FIELDS: (cysticercosis) OR ALL FIELDS: (taeniasis) OR ALL FIELDS: ('taenia solium') OR ALL FIELDS: (cestodiasis) #2 ALL FIELDS: (prevention) OR ALL FIELDS: (eradication) OR ALL FIELDS: (elimination) #3 ALL FIELDS: (program) OR ALL FIELDS: (policy) OR ALL FIELDS: (regulation) OR ALL FIELDS: (intervention) #4 ALL FIELDS: (incidence) OR ALL FIELDS: (prevalence) OR ALL FIELDS: (burden) OR ALL FIELDS: (seizure) OR ALL FIELDS: (epilepsy) OR ALL FIELDS: (morbidity) OR ALL FIELDS: (mortality) #5 #1 AND #2 AND #3 and #4

Table 2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Language	English or translated to English	Not available in English
Time period	From database inception to March 2021	NA
Study design	RCTs, non-RCTs, controlled before-after studies, uncontrolled before-after studies, interrupted time series studies, cohort studies (retrospective or prospective), cross-sectional studies with comparators	Narrative reviews, study protocols, opinion papers, theoretical papers
Population	Endemic areas of cysticercosis or *Taenia solium*	Small sample size (<100 total subjects)
Intervention	Cysticercosis or *Taenia solium* prevention programs at population level	Treatment of confirmed neurocysticercosis, laboratory research, theoretical models
Comparator	No intervention or placebo	NA
Context	Cysticercosis prevention programs to reduce incidence or prevalence of cysticercosis and adult-onset epilepsy	NA
Outcomes	Incidence or prevalence of human or porcine cysticercosis; Incidence or prevalence of adult-onset epilepsy	Outcome did not report cysticercosis incidence or prevalence (i.e., knowledge assessment only)

Abbreviations: RCT: randomized controlled trials. NA: not applicable.

Table 3. Grading of study design quality.

Grade	Design
AA	Systematic review or meta-analysis of RCTs
A	Systematic review or meta-analysis of non-RCTs RCTs or cluster RCTs
B	Systematic review or meta-analysis of controlled studies without a pretest or uncontrolled study with a pretest Non-RCT Controlled before-after study Retrospective or prospective cohort study Interrupted time series Case-control study
C	Systematic review or meta-analysis of cross-sectional studies Uncontrolled before-after study
D	Cross-sectional study
E	Case studies, case reports, narrative reviews, theoretical papers

Abbreviations: RCT: randomized controlled trials

through citation search of full texts. Inclusion and exclusion criteria are displayed in Table 2. Full texts with following characteristics were included for final analysis: (1) studies conducted at the population level, (2) outcome measured incidence or prevalence of human taeniasis or cysticercosis, (3) outcome measured incidence or prevalence of porcine cysticercosis, or (4) outcome measured incidence or prevalence of epilepsy or seizure disorders. We included incidence of porcine cysticercosis as an outcome measure as human cysticercosis manifests years after infection, which requires long-term follow up. Articles were excluded if they (1) evaluated treatment efficacy of confirmed neurocysticercosis, (2) involved less than 100 total subjects, (3) were conducted in a laboratory setting, or (4) did not report cysticercosis incidence/prevalence as a study outcome.

For final analysis of included studies, we extracted the following characteristics: country or region of the study, study periods, study design, intervention types, primary and secondary outcomes, and main results. Study periods are defined by the period from baseline prevalence measurement to the endpoint prevalence after intervention. Included studies were grouped into subcategories based on type of intervention and further underwent subgroup analysis. Quality of evidence of included studies was critically appraised based on the grading scheme provided by Shadish et al. (Table 3) [22]. This evidence grading is used to assess qualitative risk of bias of each study when evaluating reported results. The risk of bias of this systematic review is determined by the overall risk of bias of all included studies.

Results

A total of 1322 articles were identified from the initial search. Additional 49 records were found from citation search during full-text review. After removing duplicates, initial screening of titles and abstracts yielded 155 full texts, which were retrieved for in-depth review. Based on the inclusion and exclusion criteria, 34 unique studies were included for qualitative analysis (Figure 1).

From each study, we summarized characteristics including the country, income level, study design, intervention details, main results, and overall effectiveness at the end of study period (Table 4). Included studies were conducted in a total of 17 countries from Asia, Africa, North America, Central America, and South America. By income level, 11 (64.7%) of these countries were LMICs, 5 (29.4%) were upper-middle-income countries (UMICs), and 1 (5.9%) was a HIC. By number of studies, Mexico produced the most with 10 out of 34 (29.4%) studies [23–32], followed by Peru [33–36] and Tanzania [37–40], each conducting 4 (11.8%) studies. In terms of study design, there were 15 (44.1%) uncontrolled before-after studies [23,24,27,28,30,31,34,37,41–47], 10 (29.4%) randomized controlled trials (RCTs) [29,35,48] and cluster RCTs [33,38–40,49–51], 5 (14.7%) controlled before-after studies [26,32,36,52,53], and 4 (11.8%) cross-sectional studies [25,54–56]. No systematic review or meta-analysis was identified. Most studies had moderate risk of bias, giving this systematic review moderate risk of bias.

Included studies were subcategorized into six groups based on the type of intervention: 3 (8.8%) national policy [25,54,55], 3 (8.8%) community sanitation improvement [38,43,56], 3 (8.8%) health education [30,40,49], 10 (29.4%) mass drug administration (MDA)

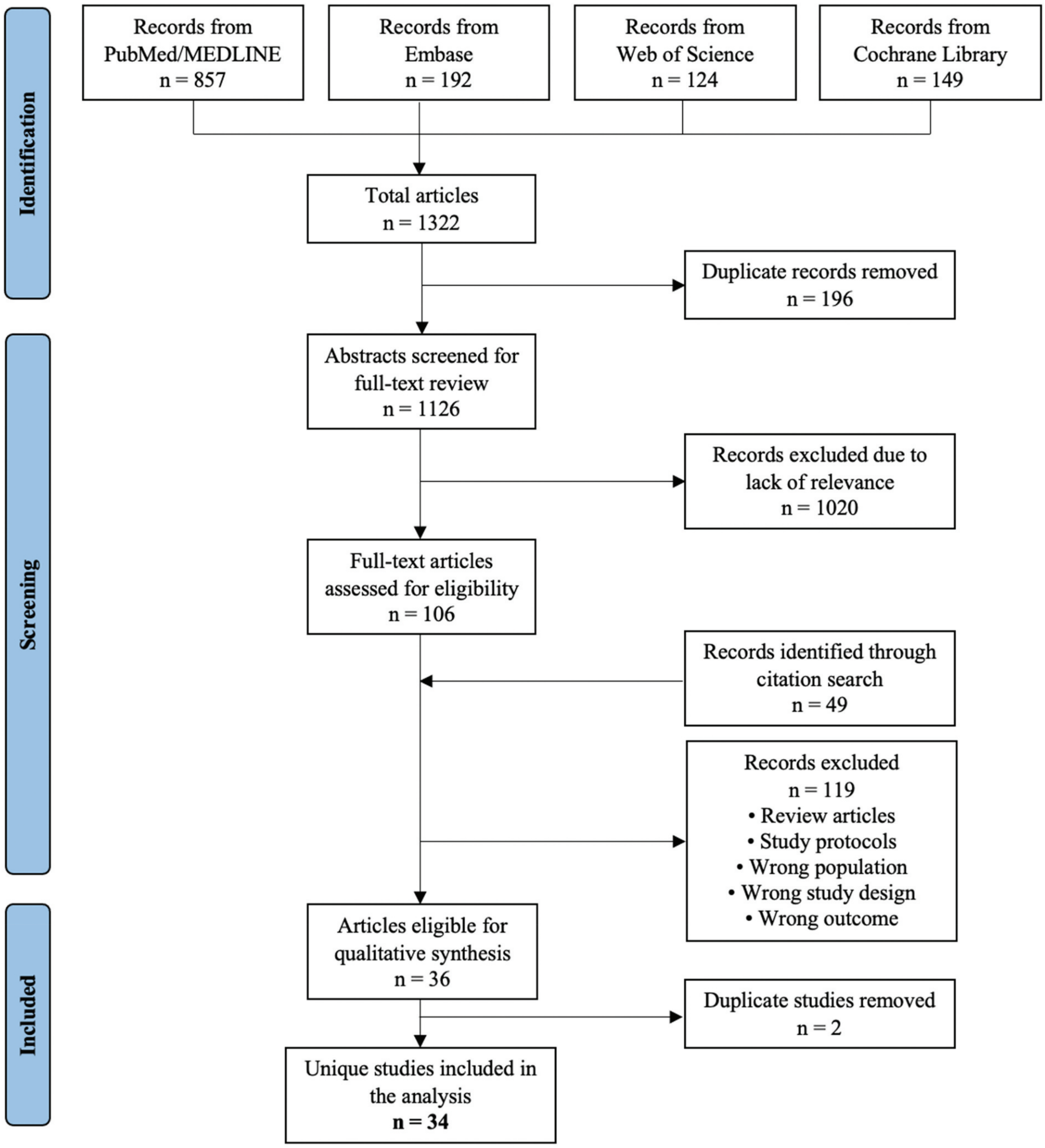

Figure 1. Flowchart of systematic search and study selection.

[24,27,31,36,37,41,42,44,46,47], 11 (32.4%) pig vaccination and treatment [26,28,29,32,35,39,48,50–53], and 4 (11.8%) combined human and pig treatment [23,33,34,45]. Overall, 28 (82.4%) studies suggested their intervention was effective in reducing cysticercosis prevalence measured at the end of study period. The lengths of study ranged from 6 months to 41 years, with a median of 1.83 years.

National policy

Three studies assessed the effect of national level programs on *Taenia spp* control [25,54,55], and two (66.7%) were effective (Table 4) [25,55]. Mandatory policies with comprehensive guidelines on public surveillance, population-wide deworming, health education, and environmental control were effective, suggested by studies in Mexico and Korea showing continuous downward trends in NCC prevalence since policy implementation [25,55]. Flisser et al. reported a significant case reduction nationally from 1995 to 2009 (1604 vs 231 cases) in Mexico and suggested *T. solium* might no longer be a public health concern [25]. Hong et al. also described a prevalence reduction in Korea from 1971 to 2012 (1.9 vs 0.04%) [55]. In Bhutan, a national policy involving school-wide deworming was only effective in short-term but not long term [54]. Schools that adhered to albendazole treatment within past 3 months before sampling showed significantly lower *T. solium* prevalence

Table 4. Studies included in systematic review by intervention types.

Study	Country	Income level	Study Design	Intervention details	Key findings	Conclusion
National policy (*n* = 3)						
Allen, 2004 [54]	Bhutan	LMIC	Cross-sectional	School-wide deworming, single dose albendazole to all school-aged children	Fecal *Taenia spp* prevalence among 5 randomly selected schools is lower in those treated in last three months compared to those not treated (0 vs 11%). Overall prevalence remains high (6.7%).	¶Effective in short-term but not in long-term
Flisser, 2010 [25]	Mexico	UMIC	Cross-sectional	Mandatory implementation national guideline published in 1994	Human cysticercosis cases national-wide decreased from 1604 to 231 cases between 1995 and 2009.	Effective
Hong, 2020 [55]	Korea	HIC	Cross-sectional	Law enforced national antiparasitic control program	Fecal *Taenia spp* prevalence decreased from 1.9% in 1971 to 0.04% in 2012.	Effective
Community-sanitation improvement (*n* = 3)						
Kabululu, 2018 [38]	Tanzania	LMIC	Cluster-RCT	I: training farmers to improve pig pens construction and feeding practice. OFZ 30 mg/kg treatment to selected pigs given at 0, 7, and 14 months.C: no treatment	No difference in porcine *T. solium* seroprevalence between intervention and control at 7 and 14 months after intervention (I vs C: 17.5 vs 21.1% and 14.7 vs 19.8%, respectively). Improved pig hygiene in intervention group. Ineffectiveness due to noncompliance of farmers and underestimation of treatment effect using serology.	Not effective
Bulaya, 2015 [43]	Zambia	LMIC	Uncontrolled before-after	Community-led total sanitation (CLTS). Trained CLTS champions lead teams to facilitate CLTS in each village	No difference in porcine cysticercosis seroincidence after intervention (pre- vs post- 13.5 vs 16.4%) Increased latrine construction post-intervention, but no change in utilization.	Not effective
Medina, 2011 [56]	Honduras	LMIC	Cross-sectional	Public health and education interventions to improve community sanitation, school-wide deworming, and community-based tract and treat	New onset epilepsy due to NCC is reduced from 36.7% of 1997 to 13.9% in 2015 ($p = 0.02$). Intervention prevented 11 new onset NCC epilepsy. Decreased prevalence of *T. solium* on stool screening (2.8 vs 0.3%).	Effective
Health education (*n* = 3)						
Carabin, 2018 [49]	Burkina Faso	LMIC	Cluster-RCT	I: Education program to improve knowledge about *T. solium* transmission (52-minute movie and comic book) and to increase community-self efficacy (Participatory Hygiene and Sanitation Transformation (PHAST)C: no treatment	Decrease in the cumulative incidence (CIR = 0.65) and prevalence (PPR = 0.84) of active human cysticercosis from baseline to after intervention. Effective in Nayala and Sanguie, but not Boulkiemde.	Effective
Ngowi, 2008 [40]	Tanzania	LMIC	Cluster-RCT	I: Education training sessions of village residents led by trained leaders and pamphlets distributionC: no treatment	Health-education effectively reduced incidence rate of porcine cysticercosis (ratio 0.57), reduced consumption of infected pork by 20%, improved knowledge about cysticercosis by 42%, but did not improve behaviors related to its transmission.	Effective
Sarti, 1997 [30]	Mexico	UMIC	Uncontrolled before-after	6-month intensive education with poster, pamphlet, and videos on cysticercosis life cycle and behavior modification	Decreased porcine cysticercosis prevalence at 1-year follow up (pre- vs post-: 2.6 vs 0% by tongue inspection, and 5.2 vs 1.2% by Ag-ELISA, $p < 0.05$). No change in prevalence of human taeniasis.	Effective

(*Continued*)

Table 4. (Continued).

Study	Country	Income level	Study Design	Intervention details	Key findings	Conclusion
Mass drug administration (n = 10)						
O'Neal, 2014 [36]	Peru	UMIC	Controlled before-after	I: tongue inspection of pigs for *T. solium* cysts every 4 months; screen stool *Taenia* antigen of all residents living within 100-meter of tongue-positive pig, treat positive individuals with single does niclosamideC: no treatment	Intervention decreased *T. solium* seroincidence by 41% compared to baseline (incidence rate ratio 0.59). No change in control group. Taeniasis prevalence is 4 times lower in intervention compared to control.	Effective
Allan, 1997 [41]	Guatemala	UMIC	Uncontrolled before-after	Single dose niclosamide MDA (75% coverage)	Decreased porcine cysticercosis prevalence compared to baseline (pre- vs post-: 55 vs 7%, $p < 10^{-6}$) at 10 month follow up. Decreased human intestinal taeniasis prevalence (3.5 vs 1.0%, $p < 0.0006$) at 10 month follow up.	Effective
Ash, 2017 [42]	Lao PDR	LMIC	Uncontrolled before-after	Two rounds of triple dose albendazole MDA (64% coverage)	Decreased *Taenia spp.* prevalence in human fecal sample by 100% after second MDA.	Effective
Braae, 2016 [37]	Tanzania	LMIC	Uncontrolled before-after	Three rounds of single dose praziquantel MDA, track-and -treat stool positive cases	Decreased human taeniasis prevalence in fecal sample (pre- vs post-: 4.1 vs 1.8%) in only one province at 36-month follow up. No difference in the other province.	Effective
Cruz, 1989 [44]	Ecuador	UMIC	Uncontrolled before-after	Single dose praziquantel MDA (74.8% coverage)	Decreased porcine cysticercosis prevalence (pre- vs post-: 11.4 vs 2.6%) at 1-year follow up.	Effective
Diaz Camacho, 1991 [24]	Mexico	UMIC	Uncontrolled before-after	Single dose praziquantel MDA (71% coverage)	Decreased human cysticercosis serum antibody (pre- vs post-:11 vs 7%).	Effective
Ramiandrasoa, 2020 [46]	Madagascar	LMIC	Uncontrolled before-after	Three rounds of single dose praziquantel MDA (95% coverage)	Significant reduction in taeniasis 4 months after the last MDA (pre- vs post-: 4.31 vs 0.68%), but taeniasis prevalence had returned to its original levels 16 months after the last MDA (4.31 vs 4.44%, $p = 0.008$).	Effective in short-term but not in long-term
Sarti, 2000 [31]	Mexico	UMIC	Uncontrolled before-after	Single dose praziquantel MDA (87% coverage)	Decreased human taeniasis seroprevalence by 53% after 6 months and by 56% after 42 months. Decreased late-onset general seizures by 70% at 42 months.	Effective
Keilbach, 1989 [27]	Mexico	UMIC	Uncontrolled before-after	Health education and single dose praziquantel (≥5 years) or niclosamide (<5 years) MDA to 60% of village residents	No reduction in porcine cysticercosis prevalence by tongue inspection at 1 year after program initiation (pre- vs post- 6.6 vs 11.0%). Knowledge did not improve.	Not effective
Steinmann, 2015 [47]	China	UMIC	Uncontrolled before-after	Health education and bi-annual albendazole MDA followed by albendazole MDA at 2-year follow up	Decreased human fecal prevalence of *Taenia spp.* by 17.5%.	Effective
Combined human and pig treatment (n = 4)						
Garcia, 2006 [33]	Peru	UMIC	Cluster-RCT	I: single dose praziquantel MDA to humans and 2 rounds of OFZ to pigsC: single dose pyrantel pamoate MDA to humans	Decreased porcine cysticercosis seroprevalence (OR 0.51) and seroincidence (OR 0.39) compared to control group.	Effective
Okello, 2016 [45]	Lao PDR	LMIC	Uncontrolled before-after	I: two rounds of albendazole MDA to humans; three rounds of vaccine and OFZ to pigsC: no treatment	Decreased human cysticercosis prevalence by 78.7%.	Effective

(*Continued*)

Table 4. (Continued).

Study	Country	Income level	Study Design	Intervention details	Key findings	Conclusion
Garcia, 2016 [34]	Peru	UMIC	Uncontrolled before-after	Three-phase intervention with each treatment period of 1-year followed by 1-year in between phases. (1) 6 interventions implemented to assess feasibility and effectiveness (2) single dose niclosamide MDA to human, single dose OFZ to pigs, and mass screening, (3) human MDA, pig MDA, and pig vaccination.	Only two intervention strategies (mass screening and mass treatment) in phase 1 were effective. One year after phase 2, 11 of 17 sampled villages had no infected pigs (live nondegenerate cysts). After phase 3, 105 of 107 villages had no infected pigs.	Effective
De Aluja, 2014 [23]	Mexico	UMIC	Uncontrolled before-after	Three rounds of pig vaccination and community education	Decreased porcine cysticercosis prevalence (pre- vs post-: 7.0 vs 0.5% by tongue inspection and 3.6 vs 0.3% by ultrasound, $p < 0.01$), and non-significant decrease in seroprevalence (pre- vs post-:17.7 to 13.3%).	Effective
Pig vaccination and treatment (n = 11)						
Pondja, 2012 [48]	Mozambique	LMIC	Randomized controlled trial	I1: single dose OFZ at 4 monthsI2: single dose OFZ at 9 monthsC: no treatment	Decreased porcine cysticercosis seroprevalence (I1 vs I2 vs C: 21.4 vs 9.1 vs 66.7%, $p < 0.01$), and total number of cysts (12.5 vs 0 vs 42.8, $p < 0.01$) in both treatment groups compared to control.	Effective
Jayashi, 2012 [35]	Peru	UMIC	Randomized controlled trial	I: single dose pig vaccine and CSF vaccine C: CSF vaccine only	Decreased porcine cysticercosis prevalence (I vs C: 16.8 vs 6.2%) and total number of cysts by 99.7% and viable cysts by 99.9% in vaccinated sentinel pigs compared to unvaccinated ones.	Effective
Morales, 2008 [29]	Mexico	UMIC	Randomized controlled trial	I: two doses pig vaccine 1 month apartC: placebo	Decreased porcine cysticercosis prevalence by 70% using tongue inspection (I vs C:13.0 vs 3.9%, $p < 0.0001$) in vaccinated group compared to control.	Effective
Chilundo, 2018 [50]	Mozambique	LMIC	Cluster-RCT	I: single dose OFZ to pigs and health education (HE)C: HE only	Porcine cysticercosis seroprevalence fluctuated throughout 2-year study period. Treatment group showed faster rate of prevalence reduction, but overall, there was no difference between treatment and control groups throughout 2 years (baseline: HE/OFZ 16% vs HE 7%, 9-month: HE/OFZ 23% vs HE 14%, 15-month: HE/OFZ 5% vs HE 9%, 24-month /endpoint: HE/OFZ 12% vs HE 9%).	Not effective
Kabululu, 2020 [39]	Tanzania	LMIC	Cluster-RCT	I: three rounds of pig vaccination and OFZ, 4 months apart C: OFZ only	Decreased porcine cysticercosis prevalence within each group (pre- vs post-: 12.0 vs 0.0% and 25.5 to 2.8%, respectively), but no difference between groups.	Effective

(*Continued*)

Table 4. (Continued).

Study	Country	Income level	Study Design	Intervention details	Key findings	Conclusion
Poudel, 2019 [51]	Nepal	LMIC	Cluster-RCT	I: four rounds of pig vaccination and OFZ, 3 months apartC: no treatment	Decreased porcine cysticercosis prevalence compared to baseline (pre- vs post-: 29.1 vs 0%, $p < 0.001$), and compared to control group (I vs C: 0 vs 17.1%, $p = 0.025$) at endpoint.	Effective
Nsadha, 2021 [53]	Uganda	LMIC	Controlled before-after	I: six rounds of pig vaccination and OFZ, 3 months apartC: no treatment	Decreased porcine cysticercosis prevalence compared to baseline (pre- vs post-: 17.2 vs 0%, $p = 0.001$), and compared to control group (I vs C: 0 vs 5.4%, $p = 0.041$) at endpoint.	Effective
Assana, 2010 [52]	Cameroon	LMIC	Controlled before-after	I: three rounds of pig vaccination and OFZ, 1 and 3 months apart C: OFZ only	Viable cysts present in control group (19.6%) but not in intervention group.	Effective
Huerta, 2001 [26]	Mexico	UMIC	Controlled before-after	I: single dose pig vaccine C: no treatment	Decreased porcine cysticercosis prevalence by 52.6% in vaccinated sentinel pigs compared to control.	Effective
Sciutto, 2007 [32]	Mexico	UMIC	Controlled before-after	I: one or two doses of pig vaccineC: no treatment	Decreased porcine cysticercosis prevalence compared to control (I vs C: 3.4 vs 10.0%) but not statistically significant ($p = 0.2$).	Not effective
Molinari, 1997 [28]	Mexico	UMIC	Uncontrolled before-after	Three doses of *T. solium* antigen extract	Decreased porcine cysticercosis prevalence by tongue inspection from baseline to second and to third inspection/ immunization (2.4 vs 1.1 vs 0.45%, $p < 0.05$)	Effective

¶Effectiveness is defined as a significant reduction of cysticercosis prevalence at the end of study period. Abbreviations: HIC: high income country. UMIC: upper middle-income country. LMIC: lower middle-income country. RCT: randomized controlled trials. I: intervention group. C: control group. MDA: mass drug administration. HE: health education. OFZ: oxfendazole. TSOL: recombinant *T. solium* antigen. CSF: classical swine fever. NCC: neurocysticercosis. ELISA: enzyme-linked immunoassay. CIR: cumulative incidence ratio. PPR: prevalence proportion ratio. OR: odd ratio.

compared to schools that did not follow treatment policy (0 vs 11.0%). Overall fecal prevalence of *T. solium* among all sampled children after 15 years of program execution, however, remained high (6.7%) [54]. This study suggests that re-infection is common; in addition, lack of other control measures such as education and environmental improvement accounts for unsustainable results.

Community sanitation improvement

Three studies implemented programs to improve sanitation at the community level, and only one (33.3%) was effective (Table 4) [56]. Two ineffective programs respectively focused on improving environmental control through pig pen construction and community-led total sanitation (CLTS), an approach addressing open defecation to achieve sustainable development goals [38,43,57]. In the pig pen construction study, the reported prevalence at 7- and 14-month after intervention were not significantly different between the intervention and control groups (17.5 vs 21.1% and 14.7 vs 19.8%, respectively) [38]. The authors attributed the ineffectiveness to noncompliance of farmers as well as low sensitivity serology tests used for diagnosis [38]. In the CLTS study, Bulaya et al. concluded that the limited study period (20 months) was insufficient to observe behavior changes that could affect *T. solium* prevalence (13.5 vs 16.4%) [43]. Although neither study was effective to reduce *T. solium* prevalence, both showed improvement in pig hygiene practice among community residents. In contrast, an 8-year program in Honduras combining public health and education interventions to improve community sanitation effectively reduced NCC-related epilepsy incidence (36.7 vs 13.9%, $p = 0.02$) and fecal *T. solium* prevalence (2.8 vs 0.3%) [56]. Specific interventions included animal husbandry training for pig farmers, construction of water projects and proper sewage disposal, construction of maternal and child health clinical, school-wide deworming, and ongoing taeniasis surveillance. This study highlights the importance of long-term interdisciplinary approach for effective *T. solium* control.

Health education

Three studies evaluated health education as the sole intervention to improve infectious source control, and all three (100.0%) were effective (Table 4) [30,40,49]. Basic knowledge on *T. solium* transmission was delivered to pig farmers and village residents and behavioral modification was encouraged. Two studies incorporated pamphlets, movies, and comic books considering various levels of literacy [30,49]. One study involved trained trainers who held small group discussions led by trained individuals to facilitate understanding [40]. Carabin et al. reported decreased cumulative incidence (ratio 0.65) and prevalence (ratio 0.84) of active human cysticercosis [49]. Ngowi et al. described reduced incidence rate of porcine cysticercosis (ratio 0.57) [40], and Sarti et al. demostrated sustained lower porcine cysticercosis prevalence (5.2 vs 1.2%) at 1-year follow up after intervention [30].

Mass drug administration

Ten studies investigated efficacy of mass drug administration to humans within an endemic area, and nine (90.0%) were found to be effective (Table 4) [24,31,36,37,41,42,44,46,47]. Among all 10, 2 studies also incorporated health education [27,47]. One study used a ring-screening strategy, in which infected pigs were identified, and humans living in close proximity were screened and treated if positive for cysticercosis [36]. The mass drug administration strategy has the advantage of eliminating *T. solium* infection from human carriers who do not present with clinical symptoms but can transmit *T. solium* eggs through outdoor defecation. The most commonly administered drug was praziquantel, reported by six studies [24,27,31,37,44,46], followed by niclosamide [36,41] and albendazole [42,47], each used in two studies. The only ineffective program was reported by Keilbach et al., in which a 1-year program combining education and mass drug administrations (MDA) did not reduced porcine cysticercosis prevalence (6.6 vs 11.0%) or improved knowledge in adults [27]. The authors concluded that the ineffectiveness of intervention was due to lack of appreciation of the disease as well as public disinterest in cysticercosis prevention. Another study by Ramiandrasoa et al. reported effectiveness of MDA after 4 months of treatment (4.31 vs 0.68%), but a rebound increase in prevalence was observed at 16-month follow-up (4.31 vs 4.44%) [46].

Pig vaccination and treatment

Eleven studies targeted pig vaccination and treatment, and nine (81.8%) demonstrated that the intervention was effective (Table 4) [26,28,29,35,39,48,51–53]. By targeting the intermediate host, pig vaccination and chemotherapy can disrupt the *T. solium* transmission cycle. Two studies did not find a statistically significant difference from the intervention [32,50]. Chilundo et al. reported that a single dose of oxfendazole (OFZ) treatment given to pigs in addition to health education (HE) resulted in greater rate of change in porcine cysticercosis seroprevalence when compared to the HE only group (HE/OFZ vs HE, baseline: 16 vs 7%, 9-month: 23 vs 14%, 15-month: 5 vs 9%, 24-month /endpoint: 12 vs 9%), but no significant difference was detected between two groups at endpoint (12 vs 9%) [50]. Additionally, the controlled before–after study by Sciutto et al. suggested that lack of statistical significance between intervention and control groups (3.4 vs 10%, p = 0.2) was due to a large difference in sample sizes between two groups [32].

Combined human and pig treatment

Four studies targeted both humans and pigs, and these were all effective (100.0%) (Table 4). Three studies treated humans with MDA or health education and pigs with either OFZ, vaccination or both [33,34,45]. Garcia et al. demonstrated the utility of combined human MDA and pig OFZ in reducing porcine cysticercosis seroprevalence (ratio 0.51) and seroincidence (ratio 0.39) [33]. Another large-scale study led by Garcia and Cysticercosis Working Group in Peru combined pig vaccination and human chemotherapy achieved *T. solium* eradication among 105 of a total 107 villages in endemic regions in Northern Peru [34]. Okello et al. from Lao People's Democratic Republic reported a decreased prevalence of human cysticercosis by 78.7% after MDA and pig vaccination and OFZ treatment [45]. One study from Mexico by De Aluja et al. which combined health education and pig vaccination indicated effective porcine cysticercosis reduction measured by tongue inspection (7.0 vs 0.5%, $p < 0.01$) but not seroprevalence (17.7 vs 13.3%) [23].

Discussion

Neurocysticercosis (NCC) accounts for a majority of adult-onset epilepsy in LMICs/UMICs with significantly lower incidence in HICs [16]. This systematic review is the first study to evaluate cysticercosis control programs utilized globally over the last few decades. We emphasize the importance of NCC disease control to reduce global disease burden of acquired epilepsy. The World Health Organization (WHO) recognizes this major public health concern and urges epilepsy control and prevention. To achieve this goal, actions must be taken. This systematic review identified 34 studies investigating the efficacy of various control programs. Of these, a vast majority (97.1%) were published from LMICs and UMICs, indicating an association between high NCC prevalence and low levels of economic development [20].

Neurocysticercosis and epilepsy

Individuals with cysticercosis develop seizures years after *T. solium* infection, with a median onset at 3–7 years [15]. Acute symptomatic seizures are often caused by cyst degeneration [14] but can also occur following resolution of cyst degeneration when parasitic larvae have died and become calcified [11]. Calcified cysts can act as epileptic foci for further seizures and increasing risk for intractable epilepsy that lasts beyond resolution of the infection [14]. It is important to note that not all patients with NCC develop epilepsy [58], and not all patients with NCC-related epilepsy have active infection. Although seizure is the most common presenting symptom of NCC, *T. solium* cysts within the CNS also cause other neurological diseases such as headaches, chronic meningitis, neuropsychiatric manifestations, and hydrocephalus [12]. Diagnosis and treatment of these sequalae require meticulous neurological evaluation, advanced imaging, and neurosurgical intervention, which may not be accessible in many *T. solium* endemic areas, underscoring the importance of effective prevention [59].

Short-term vs long-term programs

The fundamental principle of cysticercosis control is by breaking the *T. solium* transmission cycle between humans and pigs [10]. The studies identified in this review collectively summarized six major intervention types: national policy, community sanitation improvement, health education, mass drug administration, pig vaccination and treatment, and combined human and pig treatment. A majority of studies (73.5%) involved pharmacotherapy and/or pig vaccination, whereas health education, community sanitation improvement, and national policies represented a much smaller percentage (26.5%). Although pharmacotherapy provides immediate efficacy by reducing the number infected and breaking the transmission chain in short term, its effect diminishes overtime, such as in the case of reinfection, thereby requiring repeated interventions to maintain reduced prevalence [34]. In addition, praziquantel should be used with caution in individuals with cysticercosis because it causes viable intracranial cysts to degenerate, prompting potential worsening of symptoms such as seizures early on in those whom have already developed NCC [60]. On the other hand, health education and community hygiene improvement are seen here in several studies to effectively eliminate parasites in the long-term through behavior change and transmission risk reduction [61]. Improved hygiene can reduce human ingestion of tapeworm eggs from human feces, and thus controls development of human cysticercosis regardless of the infection-status of pigs and other humans in the community. These long-term interventions provide benefits beyond control of *T. solium*, as appropriate sanitation also prevents transmission of other infectious pathogens. A disadvantage is that implementation of such programs requires a higher-level of community infrastructure to ensure compliance, making it economically difficult to implement in endemic areas overlapping with poverty [20].

Context-specific consideration

Prior to selecting intervention programs, evaluating context-specific factors of the endemic regions is important [62]. As most endemic areas are indigenous rural villages, a uniform regulatory policy is unlikely to be successful. In communities with traditions of raw meat consumption and open space defecation, for example, health education plays a major role to reduce these behaviors. Second, understanding the economic structure of local pig farming is important. When comparing estimated effects of pig vaccination versus slaughterhouse regulation, vaccination provides more benefits if most of the pork is supplied by private pig farmers. The financial incentive of selling healthy meat encourages farmers to receive pig vaccination. Third, evaluating the literacy level prior to implementing intervention provides targeted education strategies and promotes adherence [30]. Various education modalities such as pamphlets distribution, movies, and small-group discussions have been shown to be effective for knowledge delivery [30,40,49]. Specific education plans should be based on the baseline knowledge of village residents. Finally, involvement of community leaders increases the likelihood for village residents to adhere and adapt to behavior changes [63]. Local leadership serves as a bridge between village residents and the district coordinator to ensure adherence. Ultimately, national policymakers should be consulted during the early stages of policy and intervention development; they should be fully informed on the far-reaching public health benefits of *T. solium* control among other competing needs [62].

Proposed plan for disease eradication

NCC is a disease of poverty. Undoubtedly, sustained disease control requires long-standing collaborative effort among individuals, local healthcare agencies, regional government, and national policymakers. In endemic areas, a stepwise approach that combines short-term ‘infectious focus’ control and long-term sustainable plans should be utilized.

As evidenced by several studies in this review, several short-term interventions are efficacious; these include mass drug administration, pig vaccination and treatment, and combined human and pig treatment. These programs rapidly decrease *T. solium* prevalence and do not involve nationwide administrative infrastructure; thus, they are particularly practical for endemic areas that require immediate action. A study in Peru using these interventions successfully eliminated cysticercosis in 105 of 107 villages [34]. However, the authors noted that the result might not be long-lasting if other measures such as health education and sanitation control were not followed.

Control and reduction of *T. solium* prevalence can take decades. Although it was a major public health problem in the 19th century, cysticercosis has been well-controlled in most developed countries [61]. Health education, sanitation improvement, and appropriate legislation are keys to the sustainability of progress. Long-term strategies include governmental purchase of infected meat, subsidies to farmers who practice clean slaughter, regulation of slaughterhouses, and increasing in public funding for community sanitary improvement [64]. Implementing these plans requires nation-wide multi-stakeholder groups and national policy makers to acknowledge the urgency of achieving cysticercosis control. There is also synergy: early implementation of long-term interventions, such as education and sanitation control, can improve efficacy of pharmacotherapy and other short-term strategies [40,43]. For example, delivering health education prior to MDA increases treatment adherence among village residents and broadens drug coverage [47]. Improving community sanitation also has major impacts on people's attitudes and willingness to pursue behavior changes. This stepwise approach provides a framework for local public health agents to implement disease control measures that could ultimately break the transmission cycle of *T. solium*.

Obstacles in control programs

Challenges exist at every step during program implementation. First, accurate assessment of local prevalence of cysticercosis in many endemic regions is difficult as differing diagnostic tests may under- or over-estimate infection rate due to varying sensitivity and specificity [12]. The best serological test for human cysticercosis is enzyme-linked immunoelectrotransfer blot (EITB) assay with a high sensitivity of 98% and low cross-reactivity [65]. Coproantigen is an inexpensive and useful tool for 'self-detection' of parasitic eggs, but the reported sensitivity is between 0 and 59% [66]. Serum antigen or antibody with ELISA is highly specific for cysticercosis with little cross-reactivity [67]. The disadvantage is that antibody persists after infection clearance, whereas antigen is only detectable in active cysticercosis [68,69]. For porcine cysticercosis, tongue inspection is an inexpensive method to quickly recognize *T. solium* cysts and has a specificity of up to 100% if carried correctly [70]. Porcine serological tests are also available, but similar limitations exist as in humans [67–69]. Selection of tests should be context-specific considering local laboratory and veterinary infrastructure. If financially allowed, combining different tests can increase reliability of results [12]. Second, the financial challenge in endemic areas warrants support from local stakeholders and national government. Within LMICs, limited economic capacity makes it difficult to allocate resources given other national priorities, such as HIV/AIDS, tuberculosis, malaria, etc. Involvement of community leaders from endemic areas is important to underscore how local needs may differ from national needs. Finally, active participation of village residents can be challenging, even though engagement of these essential stakeholder is pivotal. Underappreciation of the disease is thought to be a major barrier [27]. Health education should be a continuous theme throughout the implementation of control programs to emphasize the importance of interventions. Education should be widely delivered to encourage sanitation practice, latrine utilization, pig confinement, and other behavior changes to promote disease prevention. Involvement of community leaders is also critical to improve compliance among residents, especially with the goal of long-term integration of these health values into social norms and culture [63].

Future directions

Continued research is necessary to design cost-effective and sustainable control programs. Basic science to improve diagnostic test accuracy and accessibility should be encouraged given its pivotal role in assessing *T. solium* prevalence and tracking efficacy of prevention programs [71]. Field studies combining various intervention strategies should be conducted to select the most appropriate program that is economically acceptable and cost-effective to local and national government. Within resource limited regions, collaboration among physicians of various specialties (i.e. neurologists, neurosurgeons, primary care providers, etc.) and public health personnel with on-going international programs can provide logistical resources for building program infrastructure and reduce financial burdens [72]. Several international partnerships have been established to support the implementations of *T. solium* control programs in endemic areas such as the Pan American Health Organization (PAHO) [73], Cysticercosis Working Group in Eastern and Southern Africa (CWGESA) [74], and the Cysticercosis Working Group in Peru [34]. In addition, the WHO, the International League Against Epilepsy (ILAE), and the International Bureau for Epilepsy (IBE) have established the Global Campaign against Epilepsy in 1997 to bring the disease 'Out of the Shadows', raise public awareness about epilepsy, and reduce its health and economic impact [75]. In 2008, the launch of mental health Gap Action Programme (mhGAP) also aims to further reduce the epilepsy treatment gap [76]. LMIC policymakers are encouraged to seek assistance from international organizations to address NCC disease burdens.

Limitations

There are several limitations to this systematic review. First, only articles published in major databases are included, leading to publication bias. Studies without significant findings are less likely to be published, thus, overestimating the apparent effectiveness of interventions. Additionally, studies in a different language other than English are omitted. Effective intervention programs may exist in non-English speaking communities, but evaluation of these studies is not possible using our study design. Furthermore, most studies had moderate risk of bias, predisposing this systematic review to moderate risk of bias. Lastly, among all studies, the reported population, intervention, comparison, and outcomes, are highly heterogenous, which limits our ability to conduct meta-analysis and draw statistically significant conclusions. Nonetheless, this systematic review summarizes current cysticercosis control programs and provides valuable insights on primary epilepsy prevention in LMICs.

Conclusion

Neurocysticercosis is an important cause of preventable epilepsy predominantly affecting LMICs and populations in poverty. Unfortunately, individuals already have NCC-related epilepsy due to brain calcifications from past infection will not be helped by this work. However, through public health measures focused on *T. solium* infection prevention in endemic areas, we can reduce NCC incidence and prevent new cases of NCC-related epilepsy. Structured control programs are key to reduce its transmission of *T. solium* and therefore the incidence of epilepsy secondary to NCC. Short-term interventions such as mass drug administration, pig vaccination, and combined human and pig treatment can rapidly decrease cysticercosis prevalence. Long-term programs involving health education, community sanitation improvement, and national policies are critical to achieve sustainable results. In endemic areas, using a stepwise approach that combines short- and long-term programs promises sustained disease control. These programs must consider specific contexts of local cultures and economic development. Coordinated action among community leaders, local government, and national policymakers are encouraged to facilitate NCC-related primary epilepsy prevention.

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