

GUIDELINE for
**PREVENTIVE
CHEMOTHERAPY**
for the **CONTROL**
of *Taenia solium*
TAENIASIS

PAHO



Pan American
Health
Organization



World Health
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REGIONAL OFFICE FOR THE Americas

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Ethics and Equity Review

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ABBREVIATIONS AND ACRONYMS

ALB	albendazole
DALY	disability-adjusted life year
ELISA	enzyme linked immunosorbent assay
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MDA	mass drug administration
NICL	niclosamide
NTD	neglected tropical diseases
PAHO	Pan American Health Organization
PC	preventive chemotherapy
PICO	Population, Intervention, Comparison, Outcomes
PZQ	praziquantel
RCT	randomized controlled trial
SAE	serious adverse event
STH	soil-transmitted helminths
WASH	water, sanitation, and hygiene
WHO	World Health Organization

EXECUTIVE SUMMARY

The larval stage of the parasite *Taenia solium* can encyst in the central nervous system causing neurocysticercosis, which is the main cause of acquired epilepsy in the countries in which the parasite is endemic. Endemic areas are those with the presence (or likely presence) of the full life cycle of *T. solium*. A meta-analysis published in 2010 estimated that neurocysticercosis lesions were present at imaging in a median of 29% of patients presenting with epilepsy in endemic areas. Taeniasis/cysticercosis is recognized as the leading cause of death among all the foodborne parasitic diseases, resulting in a burden of disease that was estimated to be approximately 2.8 million disability-adjusted life years (DALYs) in 2015. The impact of taeniasis/cysticercosis also includes economic costs in people and pigs (pigs are the intermediate host), and social costs, as people with epilepsy suffer discrimination and stigma.

For a sustained and more efficient control of *Taenia solium*, a One Health approach should be used.

The parasite is most prevalent in poor and vulnerable communities in which pigs roam free, open defecation is practiced, basic sanitation is deficient, and health education is absent or limited. The disease is present mostly in Latin America, sub-Saharan Africa, and Asia.

There are several tools available for the control of *T. solium*. Preventive chemotherapy (PC) directed at the adult tapeworm is one of them. Other tools focus on pig management, pig vaccination and treatment, sanitation and hygiene, and community education. These tools can be used in combination under a One Health approach to control *T. solium*—an approach that integrates all relevant sectors and disciplines across the human-animal-environment interface to address health in a way that is more effective, efficient, or sustainable than might be achieved if not all relevant sectors were engaged.

Rationale and Target Audience

The treatment of *T. solium* taeniasis using PC is considered to be a core intervention for the control of *T. solium*, as it will have an immediate effect in reducing the risk of transmission of neurocysticercosis. However, no recommendations for the use of PC for *T. solium* taeniasis existed, and program managers and other stakeholders needed up-to-date and clear information and guidance. This Guideline for PC for the control of *T. solium* taeniasis was developed to provide that guidance. The recommendations are intended for a wide audience, including policymakers and their expert advisers, and technical and program staff at governmental institutions and organizations involved in the planning, implementation, monitoring, and evaluation of PC programs for the control of *T. solium* to improve public health.

Objectives

The objectives of the Guideline are:

1. To provide evidence-based recommendations on the appropriate choice(s) of drug and dose for preventive chemotherapy of *T. solium* in endemic areas.
2. To support the development by World Health Organization (WHO) Member States of evidence-based national preventive chemotherapy strategies for *T. solium*.
3. To inform a research priority agenda so that new evidence might contribute to stronger recommendations in any future revision of the Guideline.

These objectives are aligned with the Pan American Health Organization (PAHO) Plan of Action for the Elimination of Neglected Infectious Diseases and Post-elimination Actions 2016-2022;¹ the PAHO Disease Elimination Initiative: A Policy for an Integrated Sustainable Approach to Communicable Diseases in the Americas;² the new WHO Neglected Tropical Diseases road map 2021–2030;³ and support and contribute to achieving universal health coverage by 2030 and Goal 3.3 of the Sustainable Development Goals.

Methods

The Guideline was prepared in accordance with the latest standard WHO methods for guideline development.⁴ The WHO guideline development process involves planning; conducting a “scoping” and needs assessment; establishing an internal WHO Guideline Steering Group and an external Guideline Development Group; formulating key questions in Population, Intervention, Comparison, Outcomes (PICO) format; commissioning systematic reviews; formulation of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; writing of the guideline and planning for its dissemination and implementation. This methodology ensures that the link between the evidence base and the recommendations is transparent.

The development process included the participation of five main groups that helped guide and greatly contributed to the overall process. These included the WHO Guideline Steering Group, the Systematic Review Team, the Guideline Development Group, the External Review Group, and the WHO Guideline Review Committee. The roles and functions are described in the 2014 WHO Handbook for Guideline Development.

The evidence that informed the development of recommendations is based on a systematic review conducted as part of the guideline development process. The systematic review assessed the following research questions:

1. Should preventive chemotherapy with niclosamide (NICL), praziquantel (PZQ), or albendazole (ALB) at any dose or frequency versus no preventive chemotherapy be used for the control of taeniasis by *T. solium* in endemic populations?
2. In school-age children in areas co-endemic with *T. solium* and soil transmitted helminths, could preventive chemotherapy for these parasites be given simultaneously?

Where necessary, supplementary evidence from research and surveillance data was also sought. Pre-existing WHO information and guidance relevant to the control of *T. solium* taeniasis, soil-transmitted helminths, and schistosomiasis were also reviewed.

Recommendations were formulated by members of the Guideline Development Group after considering the balance of benefits and harms, the certainty of the evidence, values and preferences, resource implications, the feasibility of implementing the intervention, impact on equity, acceptability to stakeholders, and whether the problem was a priority.

Recommendations

The recommendations in this first edition of the Guideline for Preventive Chemotherapy for the Control of *Taenia solium* Taeniasis are conditional due to the very low certainty of the available evidence.

The recommendations include a choice of three drugs: niclosamide, praziquantel, and albendazole. The choice of drug by each country depends on different factors including co-endemicity with other diseases, drug availability, acceptability, affordability, and feasibility of implementation. Further details regarding the choice of drug are provided under implementation considerations.

¹ Pan American Health Organization. Plan of Action for the Elimination of Neglected Infectious Diseases and Post-elimination Actions 2016-2022. CD55/15 [Internet]. Washington, DC: PAHO; 2016 [cited 25 March 2021]. Available from: <https://www.paho.org/hq/dmdocuments/2016/CD55-15-e.pdf>

² Pan American Health Organization. PAHO Disease Elimination Initiative: A Policy for an Integrated Sustainable Approach to Communicable Diseases in the Americas. CE164/16 [Internet]. Washington, DC: PAHO; 2019 [cited 25 March 2021]. Available from: <https://iris.paho.org/handle/10665.2/51388>

³ World Health Organization. Ending the neglect to attain the Sustainable Development Goals – A road map for neglected tropical diseases 2021–2030. License: CC BY-NC-SA 3.0 IGO. Geneva: WHO; 2020 [cited 25 March 2021]. Available from: <https://www.who.int/publications/item/9789240010352>

⁴ World Health Organization. WHO Handbook for guideline development, 2nd ed. [Internet]. Geneva: WHO; 2014 [cited 25 March 2021]. Available from: <https://apps.who.int/iris/handle/10665/145714>

Recommendation 1

Preventive chemotherapy using **niclosamide** at 2 g (dose adjusted for children) is suggested as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations.

Conditional recommendation as a public health intervention, very low certainty evidence.

Recommendation 2

Preventive chemotherapy using **praziquantel** at 10 mg/kg bodyweight is suggested as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations, ensuring that a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

Recommendation 3

If no other alternative is available:

Preventive chemotherapy using **albendazole** at 400 mg per day for three consecutive days could be considered as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations, only if a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

Context for Recommendation 4: This is an operational recommendation to promote synergies with other PC-based public health programs. It applies once the health authorities have decided to implement PC for taeniasis in an entire community, and a school-based deworming program using ALB 400 mg single dose is already being implemented in that community. Note that PC for taeniasis is recommended for the whole community (see Implementation Consideration 1), and schools are only mentioned as one of the delivery platforms.

In the case that ALB 400 mg per day for three consecutive days is being used for PC for the control of *T. solium* taeniasis, it is also effective for soil-transmitted helminths (STH). In the case of school programs that administer PZQ 40 mg/kg for schistosomiasis and ALB 400 mg for STH, there is no need to add an additional treatment for taeniasis in those children because they are already covered by the PZQ for schistosomiasis.

Recommendation 4

In school-age children in areas co-endemic with *Taenia solium* and soil-transmitted helminths, praziquantel for taeniasis (10 mg/kg) and albendazole for soil-transmitted helminths (400 mg single dose) can be considered to be given simultaneously to promote operational synergies, ensuring that a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

The Guideline Development Group also considered in school-aged children in areas co-endemic with *T. solium* and STH, the potential combination of niclosamide for taeniasis and albendazole for STH (400 mg single dose). However, while the Guideline Development Group considered that the combination was likely to be safe due to the poor absorption of niclosamide, there was insufficient evidence to make a recommendation.

Sub-Group Considerations

For details on the sub-group considerations, please refer to Section 4.

Children

1. The dosage of niclosamide should be adjusted for children under 6 years of age.
2. Albendazole for taeniasis at 400 mg per day for three consecutive days should not be used in children below 30 kg.

People with symptoms compatible with neurocysticercosis or subcutaneous cysticercosis

3. People with symptoms compatible with neurocysticercosis (defined as a history of intense or severe and progressive headache, seizures of unknown cause, or epilepsy), or people with subcutaneous cysticercosis, should be excluded from PC with albendazole or praziquantel. It is important to be aware, however, that excluding people based on symptoms does not necessarily address the potential risk of precipitating neurological symptoms in individuals who have asymptomatic neurocysticercosis at the time of treatment.

Pregnancy

4. Pregnant women (including pregnant adolescent girls) who are in their first trimester of pregnancy, or women who are suspected to be pregnant (i.e., in early pregnancy), should be excluded from PC for taeniasis with any drug.

Implementation Considerations

For details and justification of the implementation considerations, please refer to Section 4.

Scope of preventive chemotherapy

1. PC for taeniasis should be considered for the entire community.

Food and drink

2. Praziquantel and albendazole for taeniasis should not be given with food (ideally administered at least two hours since the last meal and 30 minutes before a meal).
3. Praziquantel and albendazole for taeniasis should not be given with grapefruit juice.

Choice of drug

4. The choice of drug for PC for taeniasis should consider the presence of other co-endemic diseases that might benefit from PC.
5. The choice of drug also depends on drug availability, acceptability, affordability, and feasibility of implementation. Some drugs for PC for *T. solium* taeniasis might be available through WHO.
6. The choice of drug for PC for taeniasis should be informed by epidemiological mapping of cases based on animal (i.e., porcine cysticercosis) and human surveillance data.

Adverse events and reporting

7. Active surveillance of adverse events should be conducted for at least three days following PC for taeniasis with praziquantel or albendazole (i.e., three days after the last dose), followed by passive surveillance for at least an additional seven days.
8. The health care system at a community level needs to be trained in the recognition, reporting, and management of neurological side effects. The national program on epilepsy and other epilepsy initiatives should be included as collaborative partners.
9. Routine data collection procedures are required for standard reporting of PC coverage. Reporting should be disaggregated by age and sex, as a minimum.

Messages to the community

10. PC with any drug should be accompanied by the relevant information, education, and communication about adverse events and water, sanitation, and hygiene (WASH) messages, especially in relation to safe disposal of feces.

PC delivery

11. PC may be delivered in community facilities, health centers, schools, or other appropriate facilities, and can be integrated with other public health interventions.

Research Agenda to Support Future Updates

The research priorities to support future updates of this Guideline are detailed in Section 5 and include topics on diagnostics, PC implementation and delivery, efficacy and safety, and assessment of the value and acceptability of PC for *T. solium*.

The thresholds to trigger PC for *T. solium* taeniasis, as well as the frequency of PC for taeniasis as part of a *T. solium* control program, and the criteria to stop PC are all very important items but were beyond the remit of this Guideline and could not be included due to insufficient research evidence. They are included as Research Agenda item no. 3.

1. Introduction

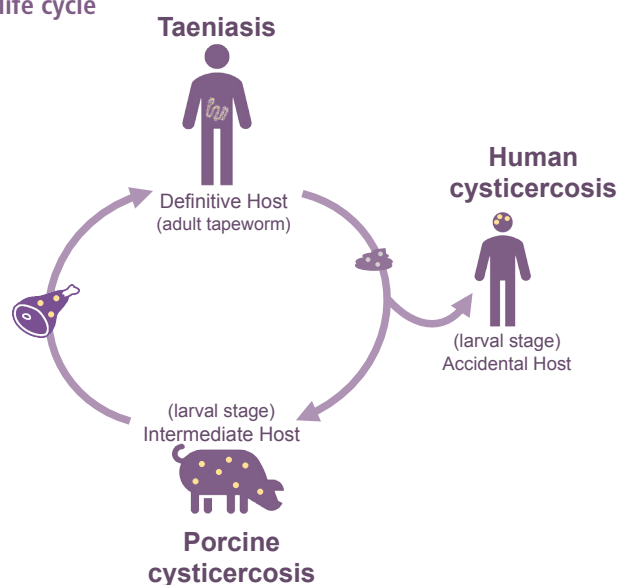
Background

Taenia solium is a zoonotic helminth parasite that infects almost exclusively humans and pigs. It causes both taeniasis (in its adult intestinal tapeworm form in humans) and cysticercosis (in its metacestode form in host tissues in humans and pigs). The parasite is present mostly in resource-limited communities in Latin America, sub-Saharan Africa, and east, south, and southeast Asia where pigs often roam free, open defecation is still practiced, basic sanitation is deficient, and health education is limited (1–4).

Cysticercosis in the central nervous system is known as neurocysticercosis and is the most important human disease caused by *T. solium*. Neurocysticercosis is the main cause of acquired epilepsy in low-income countries (5). Epilepsy is one of the most common neurological diseases and affects around 50 million people of all ages around the world (6). A meta-analysis published in 2010 estimated that neurocysticercosis lesions were present at imaging among approximately 30% of people with epilepsy in areas endemic for *T. solium* (7). In some rare instances, the proportion of neurocysticercosis among people with epilepsy has been reported to be as high as 57% and up to 70% (8; PAHO internal communication). In addition to seizures, neurocysticercosis can cause hydrocephalus, which may be fatal if not treated. Taeniasis/cysticercosis is recognized as the leading cause of death among all the foodborne parasitic diseases, and in 2015 the burden of disease due to cysticercosis was estimated to be approximately 2.8 million disability-adjusted life years (DALYs) (9). However, these may be underestimates due to limited data available from neuroimaging studies that are needed for sensitive diagnosis. The impact of taeniasis/cysticercosis also includes economic costs in people and pigs (10–15), and social costs, as people with epilepsy suffer discrimination and stigma.

The life cycle of *T. solium* includes the pig as the intermediate host (Figure 1). The *T. solium* tapeworm is acquired when people eat raw or undercooked infected pork that contains viable *T. solium* cysticerci (the larval form). These cysticerci develop to an adult tapeworm within the human intestine. The infection caused by the adult tapeworm is called taeniasis. Taeniasis due to *T. solium* is usually asymptomatic or characterized by mild and non-specific intestinal symptoms such as abdominal pain, nausea, diarrhea, or constipation.

Figure 1. *Taenia solium* life cycle



Cysticercosis is a disease resulting from infection caused by larval cysts of *T. solium* and it can occur in pigs and humans. Pigs become infected by ingesting tapeworm eggs or proglottids released in the feces of a human infected with a tapeworm. Humans acquire cysticercosis by ingesting *T. solium* eggs via the fecal-oral route, or by ingesting food or water contaminated by the feces of persons infected with *T. solium* tapeworms. The ingested eggs develop into larvae which can encyst in the muscles, skin, eyes, and the central nervous system. Sometimes, people can have both taeniasis and cysticercosis at the same time if they have been infected by both the larval form and the eggs of *T. solium*. Pigs usually do not show clinical signs, though recent research indicates that some heavily infected pigs may experience seizures (16). Porcine cysticercosis, however, can decrease the value of pigs and pork meat and often results in total condemnation of carcasses upon meat inspection (17). Taeniasis and cysticercosis caused by *T. solium* are considered by the World Health Organization (WHO) to be neglected tropical diseases. *T. solium*-endemic areas are those with the presence (or likely presence) of the full life cycle of *T. solium* (3, 18).

A variety of strategies can be used to control *T. solium* (19, 20). The WHO Expert Consultation on foodborne trematode infections and taeniasis/cysticercosis, held in Vientiane, Lao People's Democratic Republic, reported that the best options for sustainable prevention and control are (19):

Core "rapid impact" interventions:

- treatment of human taeniasis,
- mass treatment and vaccination of pigs;

Supporting measures:

- community health education,
- improved sanitation—ending open defecation;

Measures requiring more fundamental societal changes:

- improved pig husbandry—no free-roaming pigs,
- improved meat inspection, control, and handling of pork.

The treatment of *T. solium* taeniasis is considered a core intervention and will have an immediate effect in reducing the risk of transmission of neurocysticercosis. However, the treatment of taeniasis is only one component of a comprehensive *T. solium* control program. For a sustained and more efficient control of *T. solium*, a One Health approach should be used, integrating all relevant sectors and disciplines across the human-animal-environment interface, including public health and animal health (21).

Preventive chemotherapy can be an effective tool for the control of taeniasis. However, for a sustained, efficient control of *Taenia solium*, a One Health approach should be used.

Preventive chemotherapy (PC) programs can be used as a public health intervention when they have acceptable levels of efficacy and safety and can be scaled up to reach large numbers of people who are infected or at risk of infection, achieving high levels of coverage (22).

The strategy of PC can be implemented in any of three ways: (1) Mass drug administration (MDA)—administration of PC at regular intervals, irrespective of infection status, to eligible members of

entire communities in geographical areas determined to be at risk; (2) Targeted chemotherapy—administration of PC at regular intervals only to specific at-risk groups; and (3) Selective chemotherapy—administration of PC to persons who have been screened for taeniasis infection and found to be positive.

Several anthelmintics have been shown to be efficacious in the treatment of taeniasis and are currently being used in different settings (23). These include niclosamide (NICL), praziquantel (PZQ), and albendazole (ALB). All are commonly used drugs listed in the WHO Model List of Essential Medicines (21st List, 2019) as intestinal anthelmintics (24). PZQ at 40 mg/kg is used in PC for the control of schistosomiasis, clonorchiasis, and opisthorchiasis (25, 26). ALB is routinely

used in MDA and targeted PC programs to control soil-transmitted helminths (STH) (27) at a single dose of 400 mg. However, the optimal drug and dose to be used in PC for the control of *T. solium* was not known. The FAO/WHO/OIE Guidelines for the Surveillance, Prevention and Control of Taeniosis and Cysticercosis (28), published in 2005, do not include recommendations, did not use the GRADE approach to guideline development, and were not based on systematic reviews of the evidence. There were no existing recommendations for the use of PC for *T. solium* taeniosis. Program managers and all stakeholders involved need clear information to be able to select the appropriate drug for each setting and guidance on the considerations for implementation, monitoring, and evaluation. This Guideline for PC for the control of *T. solium* taeniosis was developed specifically to provide that guidance.

Note that the treatment of neurocysticercosis is a separate, complex, and specialized subject, which goes beyond the objectives of this Guideline. WHO has developed a separate guideline for the clinical management of *T. solium* neurocysticercosis (29).

Objectives

The objectives of the Guideline are:

1. To provide evidence-based recommendations on the appropriate choice(s) of drug and dose for PC of *T. solium* in endemic areas.
2. To support the development by WHO Member States of evidence-based national PC strategies for *T. solium*.
3. To inform a research priority agenda so that new evidence might contribute to stronger recommendations in a future revision of the Guideline.

These objectives are aligned with the Plan of Action for the Elimination of Neglected Infectious Diseases and Post-elimination Actions 2016-2022 approved by the Directing Council of PAHO through Resolution CD55.R9 (30); the PAHO Disease Elimination Initiative: A Policy for an Integrated Sustainable Approach to Communicable Diseases in the Americas, which sets the goals of eliminating, by 2030, more than 30 communicable diseases, including elimination of *T. solium* as a public health problem (31); the new Neglected Tropical Diseases road map 2021–2030 (32), which was endorsed by the Seventy-third World Health Assembly in November 2020; and support and contribute to achieving universal health coverage by 2030 and Goal 3.3 of the Sustainable Development Goals.

Scope

The Guideline provides evidence-based recommendations pertaining to PC for *T. solium* taeniosis in endemic human populations. Three commercially available anthelmintics that have shown efficacy in the treatment of taeniosis are included: niclosamide (NICL), praziquantel (PZQ), and albendazole (ALB). The recommendations presented in the Guideline are based on a consideration of the evidence included in a systematic review of randomized controlled trials (RCTs) and other types of trials and studies, as well as the technical knowledge and experience of the Guideline Development Group, the Guideline Steering Group, and the External Review Group (Annex 1). The Guideline is intended to support the development of evidence-based national PC strategies for the control of *T. solium*.

Outcomes of Interest

The outcomes of interest considered critical for decision-making included the following:

Infection rate with *T. solium* taeniosis, including:

- Cure rate (%), which is an indicator of the efficacy of a drug; and
- Relative reduction in prevalence (%), which is an indicator of the effectiveness of the drug in PC programs. This will be influenced by other factors such as population coverage, time of follow-up, and sampling.

Risk of side effects, including:

- Serious side effects, including neurological side effects such as seizures or severe headaches, which can be a sign of exacerbation of undiagnosed or latent neurocysticercosis;
- Mild or moderate side effects.

Other outcomes that were considered when developing recommendations included: observation time of side effects; costs, cost-effectiveness; feasibility; values and preferences of persons living in *T. solium*-endemic areas; and impact on equity.

When considering recommendations related to simultaneous treatment of both *T. solium* taeniasis and STH in school-age children, two additional outcomes were considered: infection rate with STH; and risk of side effects due to simultaneous administration/ingestion of two medicines.

The key questions and outcomes guiding the evidence review and synthesis for the recommendations in this Guideline are detailed in Section 2.

Target Audience

The recommendations contained in this Guideline are intended for a wide audience, including policymakers and their expert advisers as well as technical and program staff at governmental institutions and organizations involved in the planning, implementation, monitoring, and evaluation of PC programs for the control of *T. solium* to improve public health.

They are also intended to guide researchers and those interested in the outcomes of research to address the evidence gaps that constrain the development of strong recommendations.

Funding

The Pan American Health Organization and the World Health Organization are the sole funders of this Guideline. No other external source of funding, either from bilateral technical partners or from industry, was solicited or used.

2. Methods Used to Formulate Recommendations

WHO Guideline Development Process

The Guideline was prepared in accordance with latest standard WHO methods for guideline development (33). The WHO guideline development process involves planning; conducting a “scoping” and needs assessment; establishing an internal WHO Guideline Steering Group and an external Guideline Development Group (see Annex 1); formulating key questions in Population, Intervention, Comparison, Outcomes (PICO) format; commissioning systematic reviews; formulating recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; writing the guideline document; and planning for its dissemination and implementation. This methodology ensures that the link between the evidence base and the recommendations is transparent.

The development process included the participation of five main groups that helped guide and greatly contributed to the overall process. These included the WHO Guideline Steering Group, the Systematic Review Team, the Guideline Development Group, the External Review Group, and the WHO Guideline Review Committee. The roles and functions are described in the WHO guideline handbook (33).

WHO/PAHO Guideline Steering Group

The WHO/PAHO Guideline Steering Group was responsible for the overall coordination of the guideline development process. The Group’s tasks included drafting the scope of the Guideline and preparing the planning proposal, formulating key questions, commissioning the systematic review, identifying potential members for the Guideline Development Group and External Review Group, obtaining declarations of interests from Guideline Development Group and External Review Group members, organizing the Guideline Development Group meetings, managing any conflict of interest, submitting the finalized planning proposal to the Guideline Review Committee, reviewing the final guideline document, and submitting it to the Guideline Review Committee for review and approval.

Systematic Review Team

The Systematic Review Team performed the systematic review, evaluated the quality of evidence for each important outcome using GRADE, and drafted the Evidence to Decision frameworks. They also organized the surveys for voting to reach consensus on the Evidence to Decision frameworks, whenever appropriate.

Guideline Development Group

The Guideline Development Group (GDG) consisted of 19 members that included external experts, national Neglected Infectious Disease program managers from *T. solium*-endemic countries, and stakeholders from five of the six WHO regions (the Eastern Mediterranean Region was not included, as the disease is not a public health problem in the region). The GDG was an external body whose central task was to develop the evidence-based recommendations contained in the Guideline. This was a diverse group including relevant technical experts, professionals working in *T. solium* control from both a research and practice perspective, intended end-users, and other representatives from *T. solium*-endemic countries. Members of this group assisted in the development of the key questions in PICO format, prioritized outcomes, appraised the evidence that was used to inform the recommendations, advised on the interpretation of the evidence, formulated the recommendations and considerations, and critically reviewed the final Guideline.

External Review Group

Selected external reviewers, consisting of persons interested in the subject of the Guideline, individuals who would be affected by the recommendations, experts in systematic reviews and GRADE guidelines, and an expert in ethics and

human rights, conducted a peer review of the draft guideline document to inform revisions prior to its submission to the Guideline Review Committee for approval. The External Review Group was both geographically and gender balanced. The primary focus was to review the final guideline document and identify any errors or missing data and to comment on clarity, setting-specific issues, and implications for implementation—not to change the recommendations.

WHO Guideline Review Committee

The Guideline Review Committee was established by the WHO Director-General in 2007 to ensure that WHO guidelines are of high quality, that they are developed using a transparent and explicit process, and that, to the extent possible, recommendations are based on evidence. The Guideline Review Committee was responsible for reviewing and approving the guideline planning proposal and the final Guideline.

Management of Conflict of Interest

All members of the GDG and the Expert Review Group made declarations of interests, which were managed in accordance with standard WHO procedures. WHO forms for declaration of interests were used and these were reviewed by two members of the Guideline Steering Group. No relevant conflicts of interest were found. The Guideline Steering Group was satisfied that there had been a transparent declaration of interests. No case necessitated the exclusion of any GDG or Expert Review Group members. A summary of the declarations of interests is provided in Annex 1.

Key Questions

Two key research questions were formulated using the PICO format. For both questions a health system perspective was taken.

1. Should preventive chemotherapy with niclosamide (NICL), praziquantel (PZQ), or albendazole (ALB), at any dose or frequency versus no preventive chemotherapy be used for the control of taeniasis by *T. solium* in endemic populations?

Population: People living in *T. solium*-endemic (or suspected endemic) areas (3)

Intervention: Preventive chemotherapy with NICL, PZQ, or ALB at different doses and frequencies

Comparison: No preventive chemotherapy

Outcomes: Frequency of infection with *T. solium* taeniasis; frequency of side effects from NICL, PZQ, or ALB, including neurological effects such as seizures and severe headache in those with concurrent asymptomatic neurocysticercosis; observation time of side effects due to NICL, PZQ, or ALB.

2. In school-age children in areas co-endemic with *T. solium* and STH, could preventive chemotherapy for these parasites be given simultaneously?

Population: School-age children in areas co-endemic with *T. solium* and STH

Intervention: Preventive chemotherapy with NICL or PZQ for the control of taeniasis simultaneously with PC with ALB (400 mg in a single dose) for STH; ALB used at 400 mg for three consecutive days (triple dose) for the control of both taeniasis and STH

Comparison: NICL or PZQ alone for taeniasis; ALB 400 mg in a single dose for STH

Outcomes: Infection rate with STH; infection rate with *T. solium* taeniasis; risk of side effects due to simultaneous medication.

Context: Question 2 was designed to address the situation where a decision has been made by health authorities to implement PC for taeniasis in an entire community, and a school-based deworming program using ALB is also being implemented. In this community, in this context, could NICL or PZQ for taeniasis be given at the same time as ALB 400 mg (single dose) to the schoolchildren? It is an operational issue but requires an assessment of efficacy and safety.

Systematic Review

The evidence that informed the development of recommendations is based on a systematic review conducted as part of the guideline development process (23). Full details of the methods for the review can be found in the published review and are based on the Cochrane Collaboration Handbook for Systematic Reviews of Interventions (34). As well as the outcomes mentioned in the two key questions above, the following outcomes were included in the overall PICO criteria that guided the search strategy and selection of studies: costs, cost-effectiveness, feasibility, values and preferences of participants, and impact on equity (23).

The study designs eligible for inclusion in the review were randomized controlled trials, non-randomized controlled trials, controlled before-after studies, interrupted time series, before-after studies, repeated measures studies, and economic evaluations. Qualitative studies were only included if they provided information on the values and preferences of participants for different PC strategies or on their feasibility. Modeling studies were excluded for efficacy/effectiveness but not for economic evaluations. Case reports were not included because they have a very low level of evidence of effect, and chance cannot be ruled out (35, 36).

The following databases were searched from inception to 26 September 2018: PubMed, EMBASE, LILACS, SciELO, CAB Abstracts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessments, Epistemonikos, and 3ie—International Initiative for Impact Evaluation. In addition, Google was also searched using the same keywords. Key WHO reviews and reference lists of included studies and completed systematic reviews were scanned for any other relevant studies. Contact was made with *T. solium* experts through the GDG to identify both published and unpublished studies not found through any of the above sources. The contact persons for in-process trials registered in the WHO International Clinical Trials Registry Platform were also contacted.

The search results were screened independently by two reviewers. Two reviewers also extracted data independently and assessed the risk of bias of included studies. Differences were resolved by discussion and consensus. Data were presented as specified in the protocol and published review (23, 37). The GRADE approach to grading quality (or certainty) of evidence and strength of recommendations was used to assess the body of evidence for each PICO question and was conducted by the Systematic Review Team.

Update Search

An update search of PubMed was conducted on 16 December 2020 to check for any new studies that might meet the inclusion criteria for the systematic review. An additional 70 articles were identified and screened. The full text was obtained for seven potentially eligible studies, of which two met the inclusion criteria (38, 39). Both studies had already been brought to the attention of the GDG by experts within the GDG. Both tested PZQ 10 mg/kg in MDA and are cited in Section 3 under additional information.

Certainty of Evidence

The certainty of evidence from the systematic review was assessed for each outcome and rated on a four-point scale (Table 1), after considering the risk of bias, inconsistency, imprecision, indirectness, and publication bias (40). The terms used in the certainty assessments refer to the level of confidence in the estimate of effect (and not to the scientific quality of the investigations reviewed).

Table 1. The four classes of certainty of evidence used in GRADE

Certainty of evidence	Interpretation
High	The GDG is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The GDG is 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	The GDG's confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	The GDG has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

From Evidence to Recommendations

Recommendations were formulated by members of the GDG after considering the balance of benefits and harms, the certainty of the evidence, values and preferences, resource implications, the feasibility of implementing the intervention, impact on equity, acceptability to stakeholders, and whether the problem is a priority (41, 42). The systematic review, GRADE summary of findings tables, Evidence to Decision frameworks, and other relevant materials were provided by the Guideline Steering Group to all members of the GDG. Where necessary, supplementary evidence from research and surveillance data was also sought and provided to the GDG. Pre-existing WHO recommendations and guidance relevant to the control of *T. solium* taeniasis, STH, and schistosomiasis were also considered (27, 28, 43).

To assist the discussion of the GDG, and after the discussion of the Evidence to Decision framework by the GDG, potential recommendations were drafted by the Guideline Steering Group prior to the relevant meeting, and the methodologist provided guidance in formulating the wording and strength of the recommendations.

Given budget limitations, the GDG meetings were conducted using a virtual platform. In total, eight 2–3-hour virtual meetings were held over the course of the guideline development process, including an introductory meeting to explain the GRADE process and the Evidence to Decision frameworks. The GDG included three national Neglected Infectious Diseases program managers from *T. solium*-endemic countries in the Region of the Americas that would be responsible for implementing the Guideline. Given that language would limit their full participation in GDG meetings (Spanish was their first language), their participation and feedback was obtained in a separate process. This included translation of the most important aspects of the Evidence to Decision framework criteria, which was shared by email, and an online survey was used to obtain feedback. The results were shared with the English-speaking GDG members and incorporated into the final decision-making. Once the recommendations and implementation considerations were agreed upon by the English-speaking members, these were also translated and sent to the national program managers to obtain their feedback. The national program managers were in agreement with all aspects.

The guideline development process aimed to generate group consensus. Voting on specific points was available as an option (where a two-thirds majority of GDG members would be considered agreement) but was only used when considering the individual Evidence to Decision criteria (Annex 2). For the text and strength of each recommendation, full consensus was achieved. The final draft of the Guideline was circulated to the GDG for critical review and then to the External Review Group (Annex 1). Comments from external reviewers were incorporated into the revised Guideline as appropriate.

Strength and Interpretation of Recommendations

Each intervention recommendation was classified as strong or conditional using the following criteria:

- *Strong recommendation*: the GDG is confident that the desirable effects (benefits) of adherence to the recommendation outweigh the undesirable consequences (harms).
- *Conditional or weak recommendation*: the GDG is less certain about the balance between the benefits and harms or disadvantages of implementing a recommendation.

The interpretation of the different strengths of recommendations are:

- *Implications of a strong recommendation* for populations are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for policymakers are that the recommendation can be adopted as a policy in most situations, and for funding agencies it means the intervention probably represents an appropriate allocation of resources (i.e., large net benefits relative to alternative allocation of resources).
- *Implications of a conditional recommendation* for populations are that some people would desire PC if certain criteria were met. For policymakers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of PC as a public health intervention.

3. Evidence and Recommendations

Recommendations for Preventive Chemotherapy with Niclosamide, Praziquantel, or Albendazole for the Control of *Taenia solium* Taeniasis in Endemic Populations (Recommendations 1–3)

The recommendations include a choice of three drugs: niclosamide (NICL), praziquantel (PZQ), and albendazole (ALB). The choice of drug by each country depends on different factors including co-endemicity with other diseases, drug availability, acceptability, affordability, and feasibility of implementation. Further details regarding the choice of drug are provided under Implementation Considerations (Section 4).

Recommendation 1

Preventive chemotherapy using **niclosamide** at 2 g (dose adjusted for children) is suggested as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations.

Conditional recommendation as a public health intervention, very low certainty evidence.

Recommendation 2

Preventive chemotherapy using **praziquantel** at 10 mg/kg bodyweight is suggested as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations, ensuring that a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

Recommendation 3

If no other alternative is available:

Preventive chemotherapy using **albendazole** at 400 mg per day for three consecutive days could be considered as a public health intervention for the control of *Taenia solium* taeniasis in endemic populations, only if a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

These are conditional recommendations due to the very low certainty of evidence available for both benefits and harms.

Note: *T. solium*-endemic areas are those with the presence (or likely presence) of the full life cycle of *T. solium* (3, 18).

Summary of the Evidence for Recommendations 1–3

The evidence for the efficacy and safety of NICL, PZQ, and ALB for PC for *T. solium* taeniasis is presented in the systematic review conducted for this Guideline (23). The efficacy and safety of the following drugs and doses have been studied: ALB at both 400 mg single dose and 400 mg for three consecutive days; NICL 2 g for adults (dose adjusted for children—see Subgroup Considerations in Section 4); and PZQ at both 5 mg/kg and 10 mg/kg.

Quality of Evidence

The certainty of the evidence for the **efficacy** of NICL 2 g, PZQ 10 mg/kg, and ALB triple dose is very low due to the high risk of bias in individual studies and heterogeneity in combined estimates (Annex 3).

The certainty of the evidence for the **safety** of NICL 2 g, PZQ 10 mg/kg, and ALB triple dose is very low due to the high risk of bias in individual studies and lack of standardized monitoring practices (Annex 3).

Efficacy

There are no published studies that have directly compared the efficacy or effectiveness of the three drugs with each other (23).

A particular challenge for studies of efficacy in taeniasis is the difficulty in diagnosing *T. solium* taeniasis because tapeworm eggs (or proglottids) are only intermittently excreted in human feces (44, 45). The most common diagnostic test relies on stool microscopy, which is known to have very low sensitivity and lacks species specificity (46). Other diagnostic tests such as coproantigen ELISA or molecular tests have been developed, but these are not commercially available or have yet to be adequately validated and field-tested for large-scale use (47–49). The first coproantigen described for *T. solium* lacked species specificity (47). A later modification has been described with improved specificity for *T. solium* (48). For ALB, all included studies of efficacy used stool microscopy, which may have resulted in an overestimate of its efficacy. For NICL and PZQ, some of the efficacy studies used coproantigen ELISA, though only one study of NICL used a species-specific test (50).

Niclosamide

- NICL was only tested as a single dose of 2 g (dose adjusted for children), with a combined cure rate of 84.3% (95% CI 64.4%–99.3%) in two studies of selective chemotherapy, one of which was a before-after study (51) and the other a controlled before-after study (52) (Annex 3).
- An additional two studies tested NICL at 2 g. One of these was a before-after study of MDA with a relative reduction in prevalence of 72% (95% CI 69%–75%) (53), and the other was a controlled trial of ring-screening followed by selective chemotherapy, showing that the intervention resulted in a lower prevalence of *T. solium* at follow-up (adjusted prevalence ratio 0.28, 95% CI 0.08–0.91) compared with the no intervention area (50). Note: the baseline prevalence of taeniasis was not measured in this study.
- Results from two large-scale studies of MDA in Tumbes, Peru, however, showed lower cure rates of 63% (54) and 72% (55). It is important to note that neither of these two large-scale studies met the inclusion criteria for the systematic review due to insufficient information on methods and results.

Praziquantel

- PZQ at 5 and 10 mg/kg bodyweight was tested in two before-after studies and two controlled before-after studies of selective chemotherapy (56–59). There was no significant difference between PZQ at 5 mg/kg bodyweight (cure rate 89.0%, 95% CI 53.9%–100%, 2 studies [56, 59]) and 10 mg/kg (cure rate 99.5%, 95% CI 97.7%–100%, 4 studies [56–59]), though PZQ at 10 mg/kg tended to give better results (Annex 3).
- PZQ at 40 mg/kg was only tested in one before-after study in preschool-age children, with only three children testing positive for *Taenia* spp.; thus, it is not possible to draw reliable conclusions at this dose (60).
- PZQ at 5 mg/kg was also tested in two before-after studies of MDA but showed very variable results as shown by the wide confidence interval around the combined result (relative reduction in prevalence = 85.3%, 95% CI 0%–100%), with one study showing a relative reduction in prevalence of 100% (61) and the other 56% (62).

Albendazole

- ALB 400 mg administered in a single dose or as three doses of 400 mg given over three consecutive days was tested in two randomized controlled trials (63, 64), one controlled before-after study (65), and one before-after study (66) of selective chemotherapy (Annex 3).
- ALB 400 mg per day for three consecutive days had a significantly higher cure rate at one month follow-up than a single dose of ALB 400 mg (96.4%, 95% CI 82.8%–100%, 3 studies; vs. 52.0%, 95% CI 32.6%–71.3%, 3 studies) (63–67).
- These four studies included one randomized controlled trial (63), which showed that triple-dose ALB had a cure rate over two times that of single-dose ALB (relative risk: 2.2, 95% CI 0.7–3.7).
- Further, one controlled before-after study of single dose ALB given as annual or six-monthly MDA resulted in a relative reduction in prevalence of 55% (95% CI 45%–64%) and 23% (95% CI 15%–31%), respectively—measured approximately one year after one MDA (annual MDA) or six months after the second MDA (biannual MDA) (67).

Safety

No studies included in the systematic review reported the observation time for side effects, and it is not clear if the monitoring used in them would have detected neurological side effects.

Nicosamide

- Most studies included in the systematic review or the supplementary search for studies of side effects reported no or only mild and transient adverse events within the first three days following drug administration (23). No serious adverse events were reported.

Praziquantel

- Most studies included in the systematic review or the supplementary search for studies of side effects reported no, or only mild and transient, adverse events within the first three days following drug administration (23). One study reported that “these symptoms persisted some minutes up to 3–4 hours” (23). The only serious adverse events reported were one case of neurocysticercosis (62, 68) and another case of seizures reported following PZQ 5 mg/kg that the authors suggest may not have been directly related to the treatment (61).

Albendazole

- Most studies included in the systematic review or the supplementary search for studies of side effects reported no, or only mild and transient, adverse events within the first three days following administration of the first dose (23). One study reported that “most occurred in the morning of the third drug distribution day” (23). No serious adverse events were reported.

Additional Factors Considered for Recommendations 1–3

GDG Expert Opinion and Additional Information

Nicosamide

- NICL is poorly absorbed (69), which makes neurological side effects unlikely. In a large-scale project in Peru in which over 81,000 people were treated with NICL, adverse events were rare and mild, and no serious adverse events were reported (54, 55).

Praziquantel

- PZQ at 40 mg/kg is widely used in MDA programs for schistosomiasis and is also used for other trematodes such as clonorchiasis and opisthorchiasis, including in *T. solium*-endemic countries. From 2009 until 2018, WHO data show that approximately 530 million schoolchildren received MDA with PZQ (data reported each year in the Weekly Epidemiological Record based on data reported in the PCT Databank) (70, 71).

- Additional information was provided by the GDG member from the Ministry of Health in Madagascar. In a pilot project in Antanifotsy district, an annual round of PZQ (10 mg/kg) was conducted in 52 villages endemic for *T. solium*, for three consecutive years, from 2015 to 2017. An average of 73,769 people were treated per year. PZQ was effective, and a significant reduction in the prevalence of taeniasis was observed four months after the last MDA. However, the effect was not sustained, confirming the need for a One Health approach for a sustained control. Adverse events were monitored actively and passively by the community health agents for 5–7 days. Only mild adverse events, and no serious adverse events, were reported. This study was not available at the time of the systematic review but has been published since (39).
- However, PZQ can cross the blood-brain barrier, and so has the potential to trigger latent neurocysticercosis (61, 62, 72). Until more evidence is gathered, the GDG recommends that, when this drug is used, a reporting system is in place with active surveillance and medical referral of neurological adverse effects (see Implementation Considerations, Section 4).

Albendazole

- Additional information was provided by the Ministry of Health in Honduras. They have been implementing MDA in *T. solium*-endemic communities using ALB at 400 mg for three consecutive days, twice per year, including children from 2 years of age. Since 2015, in four communities in Lempira and Choluteca, and for one year in three communities of Cortes, 900 people of different ages in each community were treated, on average. No serious adverse events were reported. The most common adverse events reported after treatment were mild headache, nausea, and abdominal pain. People were visited every day during the administration of the ALB, and afterwards people reported the adverse events to the community health agents (that is, active surveillance for the first two days, and passive surveillance thereafter).
- While no serious adverse events were found in the studies included in the systematic review or the supplementary search for studies, there are case reports in the literature of serious central nervous system adverse events following ALB treatment for intestinal helminths in patients with latent neurocysticercosis (73–76). In 2009, the United States Food and Drug Administration requested that a precaution be included in the package insert of ALB tablets due to this possibility (https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/020666s005,s006ltr.pdf). Further, given that the monitoring period after ALB treatment considered in the studies included in the systematic review was only three days or less, the GDG could not rule out the possibility that adverse events could occur after this period.
- Given the limited experience with ALB 400 mg per day for three consecutive days in large-scale MDA programs, and that ALB can cross the blood-brain barrier and so has the potential to trigger latent neurocysticercosis (74), the GDG recommended that when this drug is used, a reporting system must be in place with active surveillance of neurological adverse events (see Implementation Considerations, Section 4) and recommended that this option should only be used when neither NICL nor PZQ are available.

Values and Preferences

The evidence found for the systematic review on values and preferences was limited (61, 63, 77–79). Thus, the members of the GDG agreed that there is possibly important uncertainty or variability in the value that populations assign to interventions to control *T. solium* taeniasis. The GDG also noted that the value people place on the outcome depends on education and that once there is education about *T. solium* and its effects, people do value the outcome. A recently published study supports this judgement, with many people stating in focus groups that they had noticed better overall health in themselves or family members since taking the treatments (PZQ), and 98% of those who completed a questionnaire would take the treatment if offered again (38).

Health Equity

There is limited evidence for the effect of PC for *T. solium* taeniasis on health equity (23). However, the GDG concluded that, by providing access to treatment and health benefits, health equity would probably be increased by PC programs for *T. solium* taeniasis, since *T. solium* taeniasis is endemic in poor and marginalized communities. These public health

intervention programs are authorized and financed by governments so that, if administered in a way that ensures access to affected populations, they provide health benefits that are equitably distributed and accrue to those most in need.

Acceptability

PC is generally widely accepted by policymakers, health workers, and teachers, based on previous experience with other large-scale PC programs (e.g., school-based PC programs for STH).

Resource Implications

The resource implications and cost-effectiveness of PC for *T. solium* taeniasis could largely only be addressed through expert opinion. No studies of cost-effectiveness were found in the systematic review and the data found on costs were not useful. Although it is recognized that such considerations should ideally be based on evidence, the research evidence was lacking at the time of writing this Guideline.

The GDG agreed that PC for *T. solium* taeniasis will probably involve moderate costs, but also acknowledged that not only the cost of the treatment itself needs to be considered, but also costs related to program planning, promotion, implementation, monitoring, evaluation, and reporting. Also, synergies with other PC programs could be sought.

Feasibility

The members of the GDG agreed that PC for *T. solium* taeniasis is feasible based on previous experience in various parts of the world, as well as the successful implementation of large-scale PC programs for STH and for schistosomiasis.

Recommendation for Preventive Chemotherapy for the Control of *Taenia solium* Taeniasis in Endemic Populations in Conjunction with School-based Preventive Chemotherapy for Soil-transmitted Helminths (Recommendation 4)

Context

Recommendation 4 is an operational recommendation, to promote synergies with other PC-based public health programs. It applies once the health authorities have decided to implement PC for taeniasis in an entire community, and a school-based deworming program using ALB 400 mg single dose for STH is already being implemented in that community. Note that PC for taeniasis is recommended for the whole community (see Implementation Consideration 1), and schools are only mentioned as one of the delivery platforms for school-age children. Other platforms/locations should be used to treat the rest of the community.

Where ALB 400 mg per day for three consecutive days is being used for PC for the control of *T. solium* taeniasis, it is also effective for STH (63, 64, 67, 79). If a program is giving two rounds of ALB for STH per year, ALB given for three consecutive days for taeniasis counts as one round for STH, and an additional round of ALB 400 mg single dose for STH would still be needed.

In the case of school programs that administer PZQ 40 mg/kg for schistosomiasis and ALB 400 mg for STH, there is no need to add an additional treatment for taeniasis in those children, because they are already covered by the PZQ for schistosomiasis.

Recommendation 4

In school-age children in areas co-endemic with *Taenia solium* and soil-transmitted helminths, praziquantel for taeniasis (10 mg/kg) and albendazole for soil-transmitted helminths (400 mg single dose) can be considered to be given simultaneously to promote operational synergies, ensuring that a reporting system is in place with active surveillance and medical referral of neurological adverse events.

Conditional recommendation as a public health intervention, very low certainty evidence.

This is a conditional recommendation due to the very low certainty of evidence available for both benefits and harms.

The GDG also considered in school-aged children in areas co-endemic with *T. solium* and STH, the potential combination of NICL for taeniasis and ALB for STH (400 mg single dose). While the GDG considered that the combination was likely to be safe due to the poor absorption of NICL, there was not enough evidence to make a recommendation.

Rationale for Recommendation 4—PZQ and ALB

Efficacy

- None of the studies included in the systematic review tested PZQ and ALB simultaneously for control of *T. solium* taeniasis and for STH (23).
- Evidence to support the efficacy of PZQ and ALB when given simultaneously is limited to one randomized controlled trial by Olds et al. (1999), which evaluated whether the concurrent administration of ALB 400 mg and PZQ 30–40 mg/kg in schoolchildren for STH and schistosomiasis affected their respective cure rates (80). The study was conducted separately in two sites in Asia (China and the Philippines) and two sites in Africa (both in Kenya). An overall total of 1,518 mostly school-age children (between 4 and 18 years of age) were enrolled and randomized into four groups: (i) PZQ + ALB 400 mg (with PZQ administered in two doses of 30 mg/kg, three hours apart in Asian sites and in one dose of 40 mg/kg in African sites); (ii) PZQ + ALB placebo; (iii) ALB 400 mg + PZQ placebo; or (iv) double placebo. It appears that most, if not all, of the children were infected with STH at baseline and that between 44.8% and 89.7% of children had schistosomes at baseline. The authors concluded that neither drug affected the cure rate of the other at 45 days follow-up.

Safety

- The trial by Olds et al. also provided information on safety (80). Adverse events were monitored actively for up to 4–6 hours post treatment and passively for up to 48 hours post treatment. It is important to note that the studies were conducted in three areas likely to be endemic for *T. solium*: Sichuan (China), Leyte (Philippines), and Kisumu (Kenya). Children receiving PZQ with or without ALB had 3.52 times the risk of having at least one side effect than children receiving ALB. The fact that side effects were more common in children with schistosomiasis suggests a strong influence of dying parasites, according to the authors. There was only one case considered to be a serious side effect, which was due to vomiting but resolved in <1 hour. The authors concluded that “combined mass treatment of schoolchildren with PZQ and ALB produced no more side effects than treatment with PZQ alone” (80). However, adverse events were only monitored for 48 hours.
- From 2009 until 2018, WHO data show that approximately 530 million schoolchildren received MDA with PZQ for schistosomiasis. It is estimated that around 99% of children would also have received ALB simultaneously based on the recommendation of WHO (81).

Quality of Evidence

- The GDG considered that the certainty of the evidence for the efficacy and safety of the simultaneous administration of PZQ 10 mg/kg and ALB 400 mg is very low due to the limited number of studies available.
- The GDG also noted the large numbers of children treated for both diseases, many in areas endemic for *T. solium*, and no clear link to serious adverse events has been noted.

Consideration of the Simultaneous Administration of NICL and ALB

The GDG noted that:

- There are no published studies on the efficacy or safety of NICL and ALB when given simultaneously.
- When administered separately, NICL 2 g (dose adjusted for children) for *T. solium* taeniasis is considered to be effective and safe (very low certainty evidence).

- While there is no research evidence to support the concurrent administration of NICL and ALB, the poor absorption of NICL suggests that there are unlikely to be significant interactions between the two drugs. Thus, it is unlikely that there would be an increased risk of side effects, including neurological side effects.

However, the GDG considered that there was not enough evidence to make a recommendation and, instead, noted it as a comment.

4. IMPLEMENTATION OF THE RECOMMENDATIONS

The GDG has provided a list of additional considerations that relate to subgroups and to the implementation of the recommendations.

Subgroup Considerations

The following considerations for different subgroups should be taken into account when implementing PC for *T. solium* taeniasis.

Children

1. The dosage of NICL should be adjusted for children under 6 years of age.

The recommended dose of NICL is (25):

- Adults: 2 g
- Children 10–35 kg: 1 g
- Children <10 kg: 0.5 g

Children <2 years of age are not usually included in PC for taeniasis, as it is unlikely that they will have a tapeworm.

2. ALB for taeniasis at 400 mg per day for three consecutive days should not be used in children below 30 kg.

This consideration is based on the expert opinion of the GDG. The reasons for including this as a subgroup consideration are the following:

The dose of ALB for treating neurocysticercosis, where the intention is for the drug to cross the blood-brain barrier, is 15 mg/kg/day divided in two or three daily doses for 10–15 days. This means that the neurocysticercosis daily ALB dose in a 30 kg child is 450 mg, which is close to the 400 mg required for taeniasis.

However, taeniasis treatment is given as a single dose, while for neurocysticercosis it is divided among 2–3 daily doses to ensure a constant dose of the active metabolite in the brain for 10–15 days. This is due to a shorter half-life of albendazole sulfoxide (ALBSO), the main active metabolite of ALB, in children than in adults. The parent drug, ALB, is not detectable even after multiple doses, and only ALBSO can be detected. A study conducted in Mexico showed that the half-life for ALBSO in children was 2.3–3.8 hours, and the mean residence time values were 5.1–13.6 hours (82), as compared to a half-life of 10–15 hours and a mean residence time of 14–20 hours in adults (83). A publication from Thailand also reports a short half-life of ALBSO, with an average of 2.5 hours (84). These results justify why, when treating children for neurocysticercosis, ALB should be administered as a divided dose, several times a day instead of only once. However, the sample size in both studies was small. Further, for the treatment of neurocysticercosis, ALB is usually given with steroids, and dexamethasone increases the plasma concentration of ALBSO, probably by decreasing the rate of elimination (85, 86). ALB for taeniasis is given only once per day and without steroids, thus possibly preventing the accumulation and effect of ALBSO on the cysts, but there is no conclusive evidence on this point.

Additional information was provided by the Ministry of Health in Honduras (see Section 3). They have been implementing MDA in *T. solium*-endemic communities and including children from 2 years of age using ALB at 400 mg for three consecutive days, twice per year. Since 2015 in four communities in Lempira and Choluteca, and for one year in three communities of Cortes, on average 900 people of different ages in each community were treated. No serious adverse events were reported. The most common adverse events that were reported after treatment were mild headache, nausea, and abdominal pain. People were visited every day during the administration of ALB, and

afterwards people reported the adverse events to the community health agents (that is, active surveillance for the first two days, and passive surveillance thereafter).

The information included above suggests that administration of ALB at 400 mg for three consecutive days in children may be safe, but the GDG preferred to take a cautious approach until more research and practice evidence was gathered.

People with Symptoms Compatible with Neurocysticercosis or Subcutaneous Cysticercosis

3. People with symptoms compatible with neurocysticercosis (defined as a history of intense or severe and progressive headache, seizures of unknown cause, or epilepsy) or people with subcutaneous cysticercosis should be excluded from PC with ALB or PZQ. It is important to be aware, however, that excluding people based on symptoms does not necessarily address the potential risk of precipitating neurological symptoms in individuals who have asymptomatic neurocysticercosis at the time of treatment.

In people with neurocysticercosis (or who potentially have neurocysticercosis because they have been exposed to *T. solium* eggs, as is the case for people with subcutaneous cysticercosis), even if the doses and regimes used for taeniasis are very different, the drugs could potentially cross the blood-brain barrier, cause the death of the parasite in brain cysts, and trigger an inflammatory response and parenchymal inflammation.

Pregnancy

4. Pregnant women (including pregnant adolescent girls) who are in their first trimester of pregnancy, or women who are suspected to be pregnant (i.e., in early pregnancy), should be excluded from PC for taeniasis with any drug.

NICL has not been shown to be mutagenic, teratogenic, or embryotoxic (25). NICL is poorly absorbed (69) but data on the use of NICL in pregnant women are limited. Therefore, the GDG decided to take a cautious approach.

PZQ has shown an apparent lack of teratogenic effects in mice, rats, and rabbits. Retrospective observations made on women inadvertently exposed to PZQ during the first trimester of pregnancy, case reports of treatment during the first trimester, and the encouraging results of over 30 years of postmarket surveillance involving many millions of doses (usually at the dose of 40 mg/kg for schistosomiasis) provide additional reassurance that PZQ is probably safe during the first trimester of pregnancy (87). However, the balance of benefits and potential harms does not justify including women in the first trimester of pregnancy for PC for taeniasis at this stage. The recently updated WHO schistosomiasis guideline recommends exclusion of pregnant women during the first trimester of pregnancy from PC with PZQ; however, lactating women can be included (88).

ALB has been found to be teratogenic at some doses in animals (89), but it is considered safe for use in humans. However, as a rule, it should not be used in women suspected to be pregnant or during the first trimester of pregnancy (90).

Implementation Considerations

When implementing PC for *T. solium* taeniasis, the following should be considered:

Scope of PC

1. PC for taeniasis should be considered for the entire community.

Taeniasis is acquired by eating raw or undercooked infected pork, so any person who has eaten poorly cooked pork is at risk. PC should not be targeted exclusively at school-age children as they are not the only at-risk group in the community. However, school platforms may be used as a component for PC delivery, to promote operational synergies. PC can be applied through MDA, targeted chemotherapy, or selective chemotherapy (see definitions in Glossary). People visiting endemic areas who eat pork might also be at risk (91).

When considering the people eligible for PC, the manufacturer recommendations should be followed.

Food and Drink

- PZQ and ALB for taeniasis should not be given with food (ideally administered at least two hours since the last meal and 30 minutes before a meal).

For schistosomiasis co-endemic areas, when using higher doses (40 mg/kg), PZQ needs to be taken with food (88). A reporting system should be in place with active surveillance and medical referral of neurological adverse events.

This consideration is to minimize absorption and decrease systemic effects and the risk of neurological side effects. The bioavailability (the fraction of the drug absorbed systemically) of ALB is poor, mainly due to its poor water solubility and consequently poor absorption. Different studies have demonstrated that giving ALB with meals increased its bioavailability (92, 93). PZQ bioavailability also increases after a high-lipid diet and a high-carbohydrate diet (94). Therefore, ALB and PZQ for taeniasis should be given in fasting conditions if possible, as that will reduce the absorption of the drugs.

- PZQ and ALB for taeniasis should not be given with grapefruit juice.

ALB maximum concentration and bioavailability can be increased by grapefruit juice (95). PZQ area under the concentration-time curve and the maximum concentration time in plasma are significantly increased by grapefruit juice (96). Therefore, to decrease PZQ and ALB systemic effects and minimize the risk of neurological adverse events, these drugs should not be given with grapefruit juice.

Choice of Drug

- The choice of drug for PC for taeniasis should consider the presence of other co-endemic diseases that might benefit from PC.

To maximize the benefits to the affected communities and the use of the limited resources available for public health programs, synergies that allow controlling several diseases simultaneously should be encouraged and promoted. The simultaneous presence of other diseases that might also benefit from PC should be considered when selecting the drug to be used, to enable those synergies and maximize the use of scarce resources. For example, areas co-endemic with schistosomiasis, clonorchiasis, or opisthorchiasis might benefit from using PZQ (at a higher dose of 40 mg/kg) as shown in Table 2.

Table 2. Examples of drug options for PC for taeniasis considering synergies with other co-endemic diseases

Target diseases	Drug options for preventive chemotherapy*		
Taeniasis only	Niclosamide (2 g)	Praziquantel (10 mg/kg)	Albendazole (400 mg per day for three consecutive days)
Taeniasis and: <ul style="list-style-type: none"> • schistosomiasis, or • clonorchiasis, or • opisthorchiasis 		Praziquantel (40 mg/kg as a higher dose is required for trematode parasites)	
Taeniasis and soil-transmitted helminths	Niclosamide (2 g) plus albendazole (400 mg, single dose) administered on separate days	Praziquantel (10 mg/kg) plus albendazole (400 mg, single dose)	Albendazole (400 mg per day for three consecutive days)

*All the stipulations and caveats included in the recommendations, subgroup, and implementation considerations must be applied.

5. The choice of drug also depends on drug availability, acceptability, affordability, and feasibility of implementation. Some drugs for PC for *T. solium* taeniasis might be available through WHO.

Availability: Some drugs might not be easily available in certain countries, even if they are included in the WHO Essential Medicines List. Drug availability depends on many factors, including drug registration, local drug production or drug imports, and import permits at country level. At the time of writing this Guideline, both NICL and PZQ are available for PC for *T. solium* taeniasis through WHO. The drugs should be requested from the WHO Regional Office by the Ministry of Health using the appropriate forms, available from the WHO website. Currently, there is no donation of ALB for PC for *T. solium* taeniasis.

Acceptability: Acceptability by key stakeholders (policymakers, health workers, affected communities) in each country might depend on previous experience with the drugs, either for *T. solium* or for other diseases. Some countries might prefer the drugs they have used previously, as they will be more familiar with their distribution, administration, conservation, and with managing potential adverse events.

Affordability: When evaluating the affordability of the different drug options, countries will need to consider the cost of the drug itself as well as any costs related to logistics, active surveillance (where this is needed), and management of potential adverse events.

Feasibility: The feasibility of implementing active surveillance and medical referral of neurological adverse events might also help countries choose between the drug options.

6. The choice of drug for PC for taeniasis should be informed by epidemiological mapping of cases based on animal (i.e., porcine cysticercosis) and human surveillance data.

In areas with a high prevalence of *T. solium* (as identified by porcine cysticercosis and human surveillance data) it is expected that there will be more cases of neurocysticercosis (see Figure 1), including latent neurocysticercosis. Latent neurocysticercosis can become symptomatic due to the natural course of the disease, or due to the side effects of the treatment received. Therefore, the absolute number of cases of neurological adverse events from using PZQ and ALB in people with latent neurocysticercosis is likely to be higher in areas with high prevalence of the disease, and NICL might be preferred.

Adverse Events and Reporting

7. Active surveillance of adverse events should be conducted for at least three days following PC for taeniasis with PZQ or ALB (i.e., three days after the last dose), followed by passive surveillance for at least an additional seven days.

This consideration was included by the GDG members due to the potential risk of neurological side effects with PZQ or ALB. While the optimal time for active surveillance of adverse events after PC with PZQ or ALB is not known, the proposed timeframe is considered to be a cautious approach until more evidence is gathered.

For NICL, because it is poorly absorbed and less likely to produce neurological side effects, the usual adverse event surveillance should be practiced.

8. The health care system at a community level needs to be trained in the recognition, reporting, and management of neurological side effects. The national program on epilepsy and other epilepsy initiatives should be included as collaborative partners.

Due to the potential risk of neurological side effects with PZQ or ALB, health care providers at community level, people monitoring adverse events, and providers of primary health care in the area need to be trained in the recognition, reporting, and management (including referral) of neurological side effects.

The country national program on epilepsy and other epilepsy initiatives (such as clinics) should be included as stakeholders or collaborative implementing partners. This might increase the quality of reporting and referral of patients with neurological adverse events.

For NICL, because it is poorly absorbed, neurological side effects are unlikely. However, because the area in which it is administered for PC will be endemic for cysticercosis, it is good practice that providers of primary health care are also familiar with neurological manifestations of cysticercosis, to provide basic case management and referral, as appropriate.

9. Routine data collection procedures are required for standard reporting of PC coverage. Reporting should be disaggregated by age and sex, as a minimum.

For data collection and coverage reporting, it is important to follow PAHO and WHO guidelines:

- Monitoring Drug Coverage for Preventive Chemotherapy (2010) <https://apps.who.int/iris/handle/10665/44400> (97)
- Preventive Chemotherapy for Neglected Infectious Diseases: Manual for the design and use of record sheets (2017) <https://iris.paho.org/handle/10665.2/34495> (98)
- Tools for Monitoring the Coverage of Integrated Public Health Interventions. Vaccination and deworming of soil-transmitted helminthiasis (2017) <https://iris.paho.org/handle/10665.2/34510> (99).

Messages to the Community

10. PC with any drug should be accompanied by the relevant information, education, and communication about adverse events and WASH messages, especially in relation to safe disposal of feces.

Information, education, and communication about adverse events should include efforts to minimize stigma related to epilepsy, to ensure that those developing neurological adverse events are not afraid to report them and that people already suffering seizures feel free to seek medical advice.

Safe disposal of feces is particularly important from the first dose of anthelmintic until 72 hours after the last dose. That is to ensure a safe disposal of the tapeworm and any tapeworm eggs, to prevent contamination of the environment, and to prevent further infection of humans and pigs.

PC Delivery

11. PC may be delivered in community facilities, health centers, schools, or other appropriate facilities, and can be integrated with other public health interventions.

Other modalities of PC delivery such as door to door can also be used.

Ethical and Equity Considerations

PC provides health benefits to populations where *T. solium* is endemic by reducing the prevalence of *T. solium* taeniasis and environmental contamination, and consequently, cases of neurocysticercosis. Populations affected by *T. solium* and neurocysticercosis are mostly poor and marginalized communities, with limited access to sanitation and to health and veterinary services (20, 28). Seizures and epilepsy, which can be caused by neurocysticercosis, can result in discrimination and stigma, which further increases suffering and marginalization among affected individuals, their families, and communities. Thus, PC for *T. solium* contributes to health equity, provided that it is given free of charge to the population, distributed to those most in need, and ethically implemented.

Public health interventions have obligations both to provide evidence-based health benefits to populations and to minimize associated harm to individuals. The evidence base on efficacy and safety, reviewed above, supports conditional recommendations for PC for *T. solium*. Because PC and other public health interventions are authorized by governments on behalf of populations, however, they must be delivered in full consultation with affected communities and with the least possible infringement on individual liberties (100).

Implementation of PC for *T. solium* raises several specific ethical considerations. First, community engagement is particularly important, as *T. solium* affects not only health, but also the economic livelihood of marginalized

communities. Further, the success of PC depends on community acceptance. Community engagement offers a vehicle to promote learning about how the implementation of the program might affect the interests of various stakeholders and use these insights to design the program in ways that take them into consideration. PC should be part of an integrated One Health approach to *T. solium* transmission control.

Second, as with vaccination, persons who participate in PC do so, at least in part, for the benefit of the community and thereby accept a certain level of risk to themselves. Consequently, governments that authorize PC have a “duty of care” for persons who are inadvertently harmed. At least 19 countries have national programs to provide financial compensation to persons who are harmed by vaccine-associated injury or disability, based on clearly defined criteria (101). Such programs are less common for neglected tropical diseases (NTDs), even though those who are the intended recipients of PC for NTDs are often the most economically marginalized. In the face of limited data on safety, compensation for unintended harm should be addressed as a key ethical component of programs using PC for *T. solium* taeniasis.

Third, informed consent for PC is a crucial ethical consideration. Informed consent includes community acceptance as well as individual assent. School-based deworming programs often use an “opt-out” consent policy, in which all children are treated unless their parents or caregivers explicitly object. This policy may be more convenient and result in higher drug coverage, but it arguably infringes on parental authority and autonomy. For PC involving children, “opt-in” policies, which require parental informed consent (whether written or otherwise), as well as assent of the child at the time of treatment, are preferable from an ethical perspective. Having a clear informed-consent procedure with an “opt-in” policy for PC for *T. solium* taeniasis might improve awareness of the population and have positive benefits for reporting of patients with adverse events.

Finally, because NTD programs are intended to address diseases of poverty, it is generally assumed that NTD programs preferentially reach and benefit those “who bear the heaviest burdens of pervasive disadvantage” (102). However, for PC, this may not always be the case (103, 104). In addition to the ethical mandate for monitoring safety and effectiveness of PC for *T. solium* taeniasis, monitoring is warranted to ensure that those who are most in need are receiving treatment.

Monitoring and Evaluation

Monitoring and evaluation should be an integral component of planning and implementing PC to assess effectiveness, to identify areas for improvement, and to account for resources used.

Both processes are aimed at measuring results to inform improvements in the management of outputs, outcomes, and impact. Monitoring requires continuous surveillance, through a systematic process, of a project or program. It involves routine data collection and reporting to determine progress made in the implementation. Monitoring helps to quickly identify the challenges during implementation, so appropriate solutions can be introduced as quickly as possible. Evaluation involves rigorous critical assessment and attribution of impacts to a project or program, to understand if the intervention has fulfilled its objectives.

Indicators used for monitoring and evaluation in a PC program can be: (a) process indicators: to determine whether organizational elements of the control program are in place and are functioning properly; (b) performance indicators: to assess whether the control program has reached the coverage goal; and (c) impact indicators: to assess whether the health impact of the control program has been reached. The recommended impact indicator for a PC program for *T. solium* taeniasis is the prevalence of *T. solium* taeniasis. It is important to note that other proxy indicators could be used, such as prevalence of porcine cysticercosis (but it is subject to more external factors that are independent of PC than the prevalence of *T. solium* taeniasis, such as better pig management and production), and in the very long term, number of neurocysticercosis cases.

The potential methods that could be used to measure the prevalence of *T. solium* taeniasis are:

- **Fecal microscopy techniques:** Although they are relatively simple and inexpensive, they have low sensitivity, do

not detect prepatent infections (as the parasite initially develops, eggs are not yet produced over an approximately 9–10-week period [44, 45]), and are not species-specific (it is not possible to distinguish *T. solium* eggs morphologically from the eggs of other tapeworms such as *T. saginata* or *T. asiatica*) (46). The latter can be overcome by collecting proglottids after treatment and identifying species by morphology (e.g., number of uterine branches) or by conducting other tests, such as copro-DNA, on the positive samples to identify the *Taenia* species.

Despite its pitfalls, microscopy can be useful. Some countries use Kato-Katz, a microscopy technique that is already used in the field to monitor other neglected parasitic diseases, as it is cheap and there are experienced staff in the majority of the endemic countries. When used for *T. solium*, a large number of samples is required, and sensitivity can be increased by doing two slides per sample. The calculation of the number of samples required should be based on the population size, estimated prevalence, and other relevant parameters.

- **Coproantigen tests:** The first tests of coproantigens that were described were not species-specific (47). Currently, species-specific tests have been described (48) but they are not commercially available. The production of in-house reagents is complex, and their validation is difficult.
- **Copro-DNA tests:** These can be very useful, since they can be specific for *T. solium*. They include tests such as copro-PCR (polymerase chain reaction) and loop-mediated isothermal amplification (LAMP). Many different variations have been published but they have not been adequately validated and field-tested for large-scale use (49). Because of the equipment and reagents needed, staff expertise, and cost, these tests can currently only be used to confirm *Taenia* species but are not accessible for routine surveillance in field programs.
- **Antibody tests:** Species-specific immunoblot assays for *T. solium* taeniasis have been described but are not widely available and have not been validated and field-tested for large-scale use. Also, it is not clear for how long they continue to give positive results after successful treatment. Therefore, they are not adequate for the monitoring of the success of a PC program. They could potentially be used as a screening test, but any positive samples would have to be confirmed as current infections. No serological test is commercially available.

During any implementation of a PC program for taeniasis, the GDG highlighted the importance of monitoring adverse events and made several remarks, detailed below. Points 1 and 2 are repeated from the Implementation Considerations, but the GDG considered them important enough to be included in both sections.

1. It is important to monitor and evaluate the occurrence of adverse events from all PC programs, and especially those administering ALB and PZQ, for neurological side effects. Active surveillance of adverse events should be conducted for at least three days following PC for taeniasis with PZQ or ALB (i.e., three days after the last dose), followed by passive surveillance for at least an additional seven days.

The neurological side effects may not occur immediately. While the optimal time for active surveillance of adverse events after PC with PZQ or ALB is not known, this timeframe was considered to be prudent until more evidence is gathered.

While NICL is poorly absorbed and neurological side effects have not been reported, the usual adverse event surveillance should be practiced. However, this does not require the same lengthy monitoring.

2. Routine data collection procedures are required for standard reporting of PC coverage. Reporting should be disaggregated by age and sex, as a minimum.

For data collection and coverage reporting, it is important to follow PAHO and WHO guidelines:

- Monitoring Drug Coverage for Preventive Chemotherapy (2010) <https://apps.who.int/iris/handle/10665/44400> (97)
- Preventive Chemotherapy for Neglected Infectious Diseases: Manual for the design and use of record sheets (2017) <https://iris.paho.org/handle/10665.2/34495> (98)
- Tools for Monitoring the Coverage of Integrated Public Health Interventions. Vaccination and deworming of soil-transmitted helminthiasis (2017) <https://iris.paho.org/handle/10665.2/34510> (99).

3. Reporting of adverse events and coverage should be conducted as per WHO manuals.

The WHO manuals dealing with monitoring and managing adverse events include:

- The Safety of Medicines in Public Health Programmes: Pharmacovigilance, an essential tool (2006) <https://apps.who.int/iris/handle/10665/43384> (105)
- Promoting Safety of Medicines for Children (2007) <https://apps.who.int/iris/handle/10665/43697> (106)
- Assuring Safety of Preventive Chemotherapy Interventions for the Control of Neglected Tropical Diseases: Practical advice for national programme managers on the prevention, detection and management of serious adverse events (2011) <https://apps.who.int/iris/handle/10665/44683> (107).
- At the time of writing this Guideline, WHO is working on a manual, training modules, and job aids to provide guidance to national NTD programs on the planning, preparation, and monitoring of the safe administration of medicine for NTDs, and to provide consolidated guidance to prevent and manage serious adverse events (SAE).

Additional useful information is available from the NTD Toolbox from USAID, Act to End NTDS, and RTI International:

- A Handbook for Managing Adverse Events Following Mass Drug Administration (AEs-f-MDA) and Serious Adverse Events (SAEs) (2015), which was created in line with suggestions from the Fifth Meeting of the Working Group on Access to Assured-Quality Essential Medicines for Neglected Tropical Diseases (WGA), WHO, Geneva, Switzerland, 26 April 2013. <https://www.ntdtoolbox.org/toolbox-search/sae-handbook-handbook-managing-adverse-events-following-mass-drug-administration-and> (108)
- Job Aids for Managing Adverse Events Following Mass Drug Administration (AEs-f-MDA) and Serious Adverse Events (SAEs). https://www.ntdenvision.org/sites/default/files/docs/sae_job_aid_packet_final.pdf

5. RESEARCH AGENDA TO SUPPORT FUTURE UPDATES

Discussions between the members of the WHO Guideline Steering Group, the Systematic Review Team, and the GDG highlighted the limited evidence available in some knowledge areas relevant to this Guideline. These areas require further research to inform future updates to the Guideline:

Diagnosics

1. Development and validation of affordable, sensitive, specific, and field-applicable diagnostic tests for *T. solium* taeniasis, neurocysticercosis, and porcine cysticercosis.
2. Comparison of taeniasis diagnostic tests to determine best practice in field conditions.

PC implementation and delivery

3. Establishment of thresholds of *T. solium* taeniasis or porcine cysticercosis to trigger PC for *T. solium* taeniasis; establishment of criteria to determine the frequency of, and when to stop, PC for *T. solium* taeniasis.
4. Qualitative studies with local communities and specific population subgroups to identify best PC practices; for example, related to community drug distributors.

Efficacy and safety

5. High quality randomized controlled trials to document the efficacy and safety of the different drugs and doses for *T. solium* taeniasis, both in comparison to placebo and in head-to-head trials:
 - Active monitoring of adverse events of PC for *T. solium* should be included as part of randomized controlled trials, observational studies, and implementation/evaluation studies.
 - Care should be taken to ensure that the trials include (and report) random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, adequately address incomplete outcome data, avoid selective reporting of outcomes, have a pre-registered/published protocol, and avoid conflict of interest.
6. Specification of optimal observation time for accurate reporting of adverse events after PC.
7. High quality randomized controlled trials to document the safety and drug interactions of the simultaneous administration of NICL or PZQ for *T. solium* taeniasis with ALB or mebendazole for STH.

Mebendazole (single 500 mg dose) can also be used in PC programs for STH control; therefore, its interactions with NICL and PZQ merit investigation.
8. Evaluation of drug combinations (such as PZQ for *T. solium* taeniasis with ALB or mebendazole for STH, and NICL for taeniasis with ALB or mebendazole for STH) in other at-risk groups, such as women of reproductive age.

Assessment

9. Value of PC for *T. solium* taeniasis to participants.
10. Economic evaluation (cost-utility, cost-effectiveness, or cost-benefit analysis) of PC for *T. solium* taeniasis, considering the impact on the community.
11. Acceptability of PC for *T. solium* taeniasis to key stakeholders, including the community.

6. DISSEMINATION AND PLANS FOR UPDATING

Dissemination

The Guideline will be published electronically in PDF format on the WHO and PAHO websites. Using electronic rather than hardcopy versions is a less expensive and faster way to provide up-to-date guidance to Member States and their implementing partners. The English language version will be made available first, with a Spanish translation soon after. Translations into French and Portuguese will be undertaken if sufficient funds are available or will be limited to translation of the executive summaries. The Guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centers, schools of public health and schools of medicine, and other United Nations agencies and nongovernmental organizations. The availability of the Guideline will be announced through PAHO social network channels (e.g., Twitter, Facebook). The Guideline will also be disseminated through webinars and through regional, subregional, and country meetings, as appropriate. Member States will be supported by WHO in the development and update of national strategies based on this Guideline. When disseminating the Guideline to Member States, the importance of engagement with the affected communities to inform implementation will be emphasized.

Updating

It is assumed that this Guideline will be valid until at least the year 2025, unless new significant evidence that requires a revision before that date arises.

User Feedback

User feedback on this first edition of the Guideline will be collected as part of all dissemination activities, both informally and by directing users to the generic PAHO NID/VT email address: eid@paho.org.

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Glossary

The definitions given below apply to the terms used in this document. They may have a different meaning in other contexts.

Adverse event: Any untoward medical occurrence that may present during treatment with a medicine but that does not necessarily have a causal relationship with this treatment. It can be caused by either administration of the drug or by a coincidental event that by chance happened after drug administration (see also Serious adverse event).

Anthelmintic: A medicine used to kill helminths (worms) and facilitate their expulsion from the human body.

Control: The reduction of disease incidence, prevalence, morbidity, and/or mortality to a locally acceptable level as a result of deliberate efforts. Continued intervention measures are required to maintain the reduction.

Disability-adjusted life years (DALYs): One DALY equals one lost year of healthy life. It is a universal metric that allows researchers and policymakers to compare different populations and health conditions across time. DALYs equal the sum of years of life lost (YLLs) and years lived with disability (YLDs).

Equity: The absence of avoidable or remediable differences among groups of people defined socially, economically, demographically, geographically, or by sex.

GRADE approach: The process of rating the quality of the best available evidence and developing health care recommendations following the approach proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.

Monitoring: The performance and analysis of routine measurements aimed at detecting changes in the health status of the population; it is a management tool. Monitoring is a part of surveillance (see Surveillance).

Monitoring and evaluation: Processes for improving performance and measuring results in order to improve management of outputs, outcomes, and impact.

One Health: A One Health approach means that all relevant sectors and disciplines across the human-animal-environment interface are involved to address health in a way that is more effective, efficient, or sustainable than might be achieved if not all relevant sectors were engaged.

Preventive chemotherapy (PC): Large-scale use of anthelmintic drugs, either alone or in combination, as a public health intervention against helminth infections. Preventive chemotherapy can be applied with different modalities:

- *Mass drug administration (MDA).* The entire population of a given administrative setting (e.g., state, region, province, district, subdistrict, village) is given anthelmintic medicines at regular intervals, irrespective of the individual infection status.
- *Targeted chemotherapy.* Specific risk groups in the population, defined by age, sex, or other social characteristics such as occupation (e.g., school-age children), are given anthelmintic medicines at regular intervals, irrespective of the individual infection status.
- *Selective chemotherapy.* After a regular screening exercise in a population group living in an area where the parasite(s) is(are) endemic, all individuals found (or suspected) to be infected are given anthelmintic medicines.

School-age children: All children between the ages of 5 and 14 years (usually), regardless of whether they are attending school. In some countries, a primary school's enrollment may include individuals of 15 years of age or older.

Serious adverse event (SAE): An adverse event that is fatal, life-threatening, disabling, or results in hospitalization or in congenital anomaly/birth defect after drug intake. It is important to distinguish between “severe” and “serious.” The term “severe” is often used to describe the intensity (severity) of a medical event, as in the grading “mild,” “moderate,” and “severe.” A severe adverse event is not necessarily serious.

Side effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in people that is related to the pharmacological properties of the drug. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no overt overdose.

Surveillance: In this Guideline, surveillance refers to the systematic collection, analysis, and interpretation of health-related data (e.g., on infection, disease, drug coverage, and adverse events) for the purpose of public health decision-making and the planning, implementation, and evaluation of NTD programs. The terms “active” and “passive” surveillance refer to the level of effort on the part of the health department to collect health-related data.

- *Passive surveillance* relies on routine reporting of health-related data, including adverse events, by health care providers, laboratories, or community members to public health departments.
- *Active surveillance* involves intensified outreach by public health agents to stimulate the reporting of health-related data; it involves an active search for cases. For adverse events and drug coverage, this may involve active community-level interviews or surveys.

Treatment coverage: In this Guideline, treatment coverage refers to drug coverage; i.e., the proportion of individuals in a defined population who received the treatment. The defined population can be: (a) a target group for treatment, e.g., school-age children; (b) the people in a geographical region, administrative area, or communities highly endemic for specific diseases; or (c) the people in an entire country. These three types of coverage are referred to as program coverage, geographical coverage, and national coverage, respectively.

Women of reproductive age: Post-menarcheal adolescent girls and adult women, including pregnant and lactating women, between the ages of 15 and 49 years.

Annex 1.

Persons Involved in Development of the Guideline

The constitution of the Guideline Development Group, Guideline Steering Group, and External Review Group follows. Also listed are members of the Systematic Review Team and the guideline methodologist. The final composition of these groups is shown as at the date of finalization of the Guideline.

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Declarations of Conflict of Interest

Guideline Development Group

- **Meritxell Donadeu** reported a potential conflict of interest related to consultancy with WHO. It was decided that the declaration did not constitute a conflict of interest.
- **Theresa Gyorkos** reported a potential conflict of interest related to grants received for research. It was decided that the declaration did not constitute a conflict of interest.
- **Andrea Sylvia Winkler** declared a potential conflict of interest related to grants received for research and consultancy with WHO. The conflict was not considered serious enough to affect Guideline Development Group membership or participation.

External Review Group

- **Ana Flisser** declared a potential conflict of interest related to money received for research from her host university. It was decided that the declaration did not constitute a conflict of interest.
- **Paul Hagan** reported a potential conflict of interest related to reimbursement of travel and subsistence expenses for WHO meetings and research advisory board meetings. It was decided that the declaration did not constitute a conflict of interest.
- **Tamara Kredo** reported a potential conflict of interest related to a grant received for research. It was decided that the declaration did not constitute a conflict of interest.

No other Guideline Development Group or External Review Group members declared a potential conflict of interest.

Annex 2.

Criteria Used in the Evidence to Decision Framework

Factors that determine the direction and strength of a recommendation

Factor	How the factor influences the direction and strength of a recommendation
Quality of the evidence	The quality of the evidence across outcomes critical to decision-making will inform the strength of the recommendation. The higher the quality of the evidence, the greater the likelihood of a strong recommendation.
Values and preferences	This describes the relative importance assigned to health outcomes by those affected by them; how such importance varies within and across populations; and whether this importance or variability is surrounded by uncertainty. The less uncertainty or variability there is about the values and preferences of people experiencing the critical or important outcomes, the greater the likelihood of a strong recommendation.
Balance of benefits and harms	This requires an evaluation of the absolute effects of both benefits and harms (or downsides) of the intervention and their importance. The greater the net benefit or net harm associated with an intervention or exposure, the greater the likelihood of a strong recommendation in favor or against the intervention.
Resource implications	This pertains to how resource-intense an intervention is, whether it is cost-effective and whether it offers any incremental benefit. The more advantageous or clearly disadvantageous the resource implications are, the greater the likelihood of a strong recommendation either for or against the intervention.
Priority of the problem	The problem's priority is determined by its importance and frequency (i.e., burden of disease, disease prevalence, or baseline risk). The greater the importance of the problem, the greater the likelihood of a strong recommendation.
Equity and human rights	The greater the likelihood that the intervention will reduce inequities, improve equity, or contribute to the realization of one or several human rights as defined under the international legal framework, the greater the likelihood of a strong recommendation.
Acceptability	The greater the acceptability of an option to all or most stakeholders, the greater the likelihood of a strong recommendation.
Feasibility	The greater the feasibility of an option from the standpoint of all or most stakeholders, the greater the likelihood of a strong recommendation. Feasibility overlaps with values and preferences, resource considerations, existing infrastructures, equity, cultural norms, legal frameworks, and many other considerations.

Annex 3.

GRADE Tables Assessing the Certainty of the Evidence

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Preventive Chemotherapy for the Control of Taeniasis by *Taenia solium* in Endemic Populations

A. Preventive chemotherapy with NICL at 2 g (adjusted for children) compared with no intervention—infection rate with *Taenia solium taeniasis*

Patient or population: the control of taeniasis by *Taenia solium* in endemic populations

Setting: endemic populations

Intervention: preventive chemotherapy with NICL at 2 g (adjusted for children)

Comparison: no intervention

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Infection rate with <i>T. solium</i> taeniasis—cure rate	106 (2 observational studies) ^a	⊕○○○ VERY LOW ^{b,c}	cure rate (%) 84.3 (64.4 to 99.3)
Infection rate with <i>T. solium</i> taeniasis—relative reduction in prevalence	1,116 (1 observational study) ^d	⊕○○○ VERY LOW ^e	relative reduction in prevalence (%) 72 (69 to 75)
Infection rate with <i>T. solium</i> taeniasis—prevalence at follow-up (intervention vs. control) ^f	1,258 (1 observational study) ^g	⊕○○○ VERY LOW ^h	prevalence ratio 0.28 (0.08 to 0.91)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval

Explanations

^a Includes one before-after study (51) and one controlled before-after study (52) (with NICL arm treated separately).

^b Downgraded for risk of bias (both studies assessed as high risk).

^c Downgraded for inconsistency: considerable heterogeneity in results ($I^2 = 85\%$).

^d Includes one before-after study (53).

^e Downgraded for risk of bias (bias in selection of participants into the study, incomplete outcome data not addressed).

^f This study did not measure baseline prevalence of taeniasis. Only the prevalence at follow-up in both intervention (ring-screening then selective chemotherapy) and control groups are reported and compared.

^g Study design: controlled trial (no baseline measure for taeniasis) (50).

^h Downgraded for risk of bias (lack of random sequence generation, no allocation concealment, baseline outcome measures not similar, incomplete outcome data not addressed).

For details of studies included in the review, see Haby et al. (2020) (23).

*B. Preventive chemotherapy with PZQ at 10 mg/kg bodyweight or 5 mg/kg compared with no intervention—infection rate with *Taenia solium taeniasis**

Patient or population: the control of taeniasis by *Taenia solium* in endemic populations

Setting: endemic populations

Intervention: preventive chemotherapy with PZQ at 10 mg/kg bodyweight or 5 mg/kg

Comparison: no intervention

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Infection rate with <i>T. solium</i> taeniasis—cure rate (PZQ 10 mg/kg)	148 (4 observational studies) ^a	⊕○○○ VERY LOW ^b	cure rate (%) 99.5 (97.7 to 100.0)
Infection rate with <i>T. solium</i> taeniasis—cure rate (PZQ 5 mg/kg)	35 (2 observational studies) ^c	⊕○○○ VERY LOW ^{d,e}	cure rate (%) 89.0 (53.9 to 100.0)
Infection rate with <i>T. solium</i> taeniasis—relative reduction in prevalence (PZQ 10 mg/kg)	(0 studies)	--	not estimable
Infection rate with <i>T. solium</i> taeniasis—relative reduction in prevalence (PZQ 5 mg/kg)	1,144 (2 observational studies) ^f	⊕○○○ VERY LOW ^{g,h,i}	relative reduction in prevalence (%) 85.3 (0.0 to 100.0)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval

Explanations

^a Included two controlled before-after studies (56, 59) and two before-after studies (57, 58).

^b Downgraded for risk of bias. For the two studies with a control group there was: lack of random sequence generation, no allocation concealment, unclear as to blinding of participants, personnel and outcome assessors, and one study was authored and funded by the manufacturer of PZQ. For the two before-after studies there was: bias in selection of participants into the study, and unclear as to blinding of outcome assessors.

^c Both studies were controlled before-after studies (56, 59).

^d Downgraded for risk of bias: lack of random sequence generation, no allocation concealment, unclear as to blinding of participants, personnel and outcome assessors, and one study was authored and funded by the manufacturer of PZQ.

^e Downgraded for inconsistency: considerable heterogeneity in results ($I^2 = 77\%$).

^f Both studies were before-after studies (61, 62).

^g Downgraded for risk of bias: both studies scored high risk on three items each, including incomplete outcome data not addressed.

^h Downgraded for inconsistency: considerable heterogeneity in results ($I^2 = 100\%$).

ⁱ Downgraded for imprecision: very wide confidence intervals.

For details of studies included in the review, see Haby et al. (2020) (23).

C. Preventive chemotherapy with ALB 400 mg given for three consecutive days (triple dose) or ALB 400 mg as a single dose compared with no intervention—infection rate with *T. solium* taeniasis

Patient or population: the control of taeniasis by *Taenia solium* in endemic populations

Setting: endemic populations

Intervention: preventive chemotherapy with ALB 400 mg given for three consecutive days (triple dose) or ALB 400 mg as a single dose

Comparison: no intervention

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Infection rate with <i>Taenia</i> spp. taeniasis—cure rate (RCT, triple dose vs. single dose)	68 (1 RCT)	⊕⊕○○ LOW ^{a,b}	RR 2.2 (0.7 to 3.7)
Infection rate with <i>Taenia</i> spp. taeniasis—cure rate (single dose ALB 400 mg)	185 (3 observational studies) ^c	⊕○○○ VERY LOW ^{d,e}	cure rate (%) 52.0 (32.6 to 71.3)
Infection rate with <i>T. solium</i> taeniasis—cure rate (triple dose ALB 400 mg)	161 (3 observational studies) ^f	⊕○○○ VERY LOW ^{g,h}	cure rate (%) 96.4 (82.8 to 100.0)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

Explanations

^a Risk of bias: lack of blinding of participants and personnel, selective outcome reporting (63).

^b Very wide confidence intervals.

^c Includes one controlled before-after study (65) (with each arm treated separately) and two RCTs (63, 64) (with ALB 400 mg arm treated separately).

^d Downgraded for risk of bias: for the two RCTs, blinding of participants and personnel and selective outcome reporting; for the controlled before-after study, lack of random sequence generation, no allocation concealment and study was authored and funded by the manufacturer of ALB.

^e Downgraded for inconsistency: considerable heterogeneity in results ($I^2 = 60\%$).

^f Includes one RCT (63) and one controlled before-after study (65) (with ALB triple dose arm treated separately) and one before-after study (66).

^g Downgraded for risk of bias: for the RCT, blinding of participants and personnel and selective outcome reporting; for the controlled before-after study, lack of random sequence generation, no allocation concealment and study was authored by the manufacturer of ALB; for the before-after study, bias in selection of participants into the study, incomplete outcome data not addressed, selective outcome reporting and potential conflict of interest.

^h Downgraded for inconsistency: considerable heterogeneity in results ($I^2 = 79\%$).

For details of studies included in the review, see Haby et al. (2020) (23).

D. Preventive chemotherapy with NICL, PZQ, or ALB at any dose or frequency compared with no intervention—side effects

Patient or population: the control of taeniasis by *Taenia solium* in endemic populations

Setting: endemic populations

Intervention: preventive chemotherapy with NICL, PZQ, or ALB at any dose or frequency

Comparison: no intervention

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Risk of side effects from NICL, PZQ, or ALB, including seizures and severe headache follow-up: range 1–3 days	17,951 (11 observational studies) ^a	⊕○○○ VERY LOW ^b	Most studies reported either no or only mild and transient side effects within the first three days following drug administration (drugs studied included ALB 400 mg single and triple dose, NICL 2 g, PZQ 40 mg/kg, PZQ 5 mg/kg, PZQ 10 mg/kg). One case of neurocysticercosis diagnosed following severe headaches (following PZQ 5 mg/kg) and one case of seizures (following PZQ 5 mg/kg) that the authors suggest may not have been directly related to the treatment.
Observation time of side effects due to NICL, ALB, or PZQ	(0 observational studies)	--	No studies included in the systematic review reported this outcome. However, authors of two studies made specific comments on the timing of side effects: "These symptoms persisted some minutes up to 3–4 hours" (PZQ 5 or 10 mg/kg) and "most occurred in the morning of the third drug distribution day" (ALB).

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval

Explanations

^a A variety of designs included (four before-after, five controlled before-after, two RCTs) but none compared the drug to placebo or no intervention (52, 56, 58, 59, 61–65, 79, 109).

^b Downgraded for risk of bias in individual studies and lack of standardized monitoring practices.

Note: The studies that met the inclusion criteria for the systematic review only had 1–3 days of follow-up for this outcome. One-day follow-up might not be sufficient to assess neurological side effects.

For details of studies included in the review, see Haby et al. (2020) (23).

Preventive Chemotherapy in School-age Children for Simultaneous Treatment of Both *Taenia solium* Taeniasis and Soil-transmitted Helminths

E. Preventive chemotherapy with ALB 400 mg given for three consecutive days (triple dose) compared with ALB 400 mg (single dose) in school-age children

Patient or population: the control of both taeniasis by *Taenia solium* and soil-transmitted helminths in school-age children

Setting: endemic populations

Intervention: preventive chemotherapy with ALB 400 mg given for three consecutive days (triple dose)

Comparison: ALB 400 mg (single dose)

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Infection rate with soil-transmitted helminths (hookworm)	105 (1 RCT)	⊕⊕○○ LOW ^{a,b}	difference in cure rates (%) 22.9 (8.6 to 37.2) ^c
Infection rate with soil-transmitted helminths (<i>T. trichiura</i>)	141 (1 RCT)	⊕⊕○○ LOW ^{a,b}	difference in cure rates (%) 22.4 (4.3 to 40.5) ^d
Infection rate with soil-transmitted helminths (<i>A. lumbricoides</i>)	113 (1 RCT)	⊕⊕⊕○ MODERATE ^a	difference in cure rates (%) 0.7 (-5.4 to 6.8) ^e
Infection rate with <i>Taenia</i> spp. taeniasis	150 (1 RCT)	⊕⊕○○ LOW ^{a,b}	difference in cure rates (%) 55 (26 to 84) ^f

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomized controlled trial

Explanations

^a Risk of bias: lack of blinding of participants and personnel, selective outcome reporting (63).

^b Downgraded for imprecision: very wide confidence interval.

^c Cure rate: 92.0% (95% CI: 80.8%–97.8%), (46/50) for triple dose; 69.1% (95% CI: 55.2%–80.9%), (17/55) for single dose.

^d Cure rate: 56.2% (95% CI: 41.2%–70.5%), (27/48) for triple dose; 33.8% (95% CI: 22.6%–46.6%), (22/65) for single dose.

^e Cure rate: 96.8% (95% CI: 89.0%–99.6%), (61/63) for triple dose; 96.1% (95% CI: 89.1%–99.2%), (75/78) for single dose.

^f Cure rate: 100% for triple dose (7/7); 45% for single dose (5/11).

For details of studies included in the review, see Haby et al. (2020) (23).

The larval stage of the parasite *Taenia solium* can encyst in the central nervous system causing neurocysticercosis, which is the main cause of acquired epilepsy in the countries in which the parasite is endemic. Endemic areas are those with the presence (or likely presence) of the full life cycle of *Taenia solium*. The parasite is most prevalent in poor and vulnerable communities in which pigs roam free, open defecation is practiced, basic sanitation is deficient, and health education is absent or limited.

Several tools are available for the control of *Taenia solium*. Preventive chemotherapy for *Taenia solium* taeniasis, which is directed at the adult tapeworm, is one of them. Other tools focus on pig management, pig vaccination and treatment, sanitation and hygiene, and community education.

Three potential drugs—niclosamide, praziquantel, and albendazole—have been considered for use for preventive chemotherapy in *Taenia solium* taeniasis control programs through mass drug administration or targeted chemotherapy. In this Guideline, we provide recommendations for preventive chemotherapy in *Taenia solium*-endemic areas using niclosamide, praziquantel, or albendazole, including at which dose and in which population groups. The development of this Guideline is based on the latest standard World Health Organization methods for guideline development, including the use of systematic search strategies, synthesis, quality assessment of the available evidence to support the recommendations, and participation of experts and stakeholders in the Guideline Development Group and External Review Group. The recommendations are intended for a wide audience, including policymakers and their expert advisers, and technical and program staff at governmental institutions and organizations involved in the planning, implementation, monitoring, and evaluation of preventive chemotherapy programs for the control of *Taenia solium*.

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