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Effectiveness of public health interventions in reducing the prevalence of *Opisthorchis viverrini*: a protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction The carcinogenic liver fluke *Opisthorchis viverrini* is a major public health problem in the Mekong basin region. The liver flukes can induce cholangiocarcinoma, a bile duct cancer that causes a significant burden of mortality and economic loss. Various public health interventions have been conducted to reduce opisthorchiasis but the prevalence of *O. viverrini* remains high in endemic regions. The aim is to quantify the effectiveness of public health interventions in reducing the prevalence of *O. viverrini* infection.

Methods and analysis Seven databases (including PubMed, SCOPUS, Web of Science, EMBASE, ScienceDirect, Thai thesis database and TCI (Thai journals online)) will be searched from initiation through to 2022 to identify studies of interventions to reduce the prevalence of *O. viverrini* infection. The prevalence, incidence or number of *O. viverrini*-infected people will be used as the source of *O. viverrini* prevalence data. A conventional meta-analysis and a Bayesian network meta-analysis will be conducted to undertake direct and indirect comparisons of different interventions. Meta-regression will be used to determine the effect of each intervention. The risk of bias will be assessed using the Cochrane Collaboration's risk of bias tool. Heterogeneity between studies will be determined by forest plots and I^2 and publication bias investigated with funnel plots and the Egger's test.

Ethics and dissemination Ethical approval will not be required because this study will only use published data. The final report of this review will be disseminated through publication in a peer-reviewed scientific journal and will also be presented at relevant conferences.

PROSPERO registration number CRD42022323066.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will conduct the first systematic review and network meta-analysis to investigate the effectiveness of public health interventions in reducing the prevalence of *Opisthorchis viverrini*.
⇒ The systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ The study screening, data extraction and assessment of the risk of bias will be performed independently by two authors and disagreements will be resolved by a third author.
⇒ The quality of the studies included in the systematic review will be evaluated and the quality of the evidence will be assessed using the Cochrane risk of bias tool.

INTRODUCTION

The liver fluke *Opisthorchis viverrini* is a food-borne trematode that can cause cholangiocarcinoma (CCA). The parasite is distributed throughout the Mekong basin in Southeast Asia, where more than 10 million people are infected.[1] The life cycle of *O. viverrini* is complex, involving aquatic snails of the genus *Bithynia* spp as a first intermediate host and cyprinid fish as a second intermediate host. Humans are the definitive host of the parasite and become infected after eating undercooked fish products.[2]

The prevalence of *O. viverrini* throughout the Mekong basin regions has not been established via national surveys except in Thailand, and in schoolchildren in Laos and Cambodia.[1] The prevalence in Laos ranged from 17% to 88.7%,[3–5] whereas in Vietnam, the prevalence ranged from 15.2% to 36.9%.[1] In Cambodia, data have been collected in a few provinces with prevalence ranging from 0% to 47.5%.[6] In Myanmar, data have been reported from a small area in which overall prevalence was found to be 9.3%.[7] Only Thailand has implemented an intensive national liver fluke control campaign, which has been driven by the Thai Ministry of Public Health for decades. The nationwide prevalence of liver fluke infection decreased from over 15% in 1996 to 2.2% in 2019.[8] The national

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programme aimed to eliminate liver fluke infection in Thailand by 2025.[1]

Interventions for *O. viverrini* infection are multifaceted, being targeted at different stages of the parasite life cycle. Anthelmintic drugs are used to control infection by killing adult worms in the human host and animal reservoirs. However, the reinfection rate of *O. viverrini* had been high, and efforts have been made to design new, sustainable interventions.[9 10] Sustainable control involves multiple options such as health education, improved sanitation and ultrasound screening, in addition to mass drug administration. However, the most effective intervention or combination of interventions remains unknown.

This systematic review will systematically search the literature for evidence regarding the effectiveness of *O. viverrini* interventions and seek to measure the effectiveness of interventions in reducing infections in humans using network meta-analysis methods. The outcomes of this study will be important for policymakers to design sustainable prevention and control programmes for *O. viverrini* in endemic countries such as Thailand, Laos, Cambodia and central and southern Vietnam.

METHODS

We have developed this systematic review and network meta-analysis protocol according to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses Protocols 2015 guidelines (see online supplemental table S1)[11] (figure 1) . The study will commence in August 2022 and we plan to end it in November. This information is now provided.

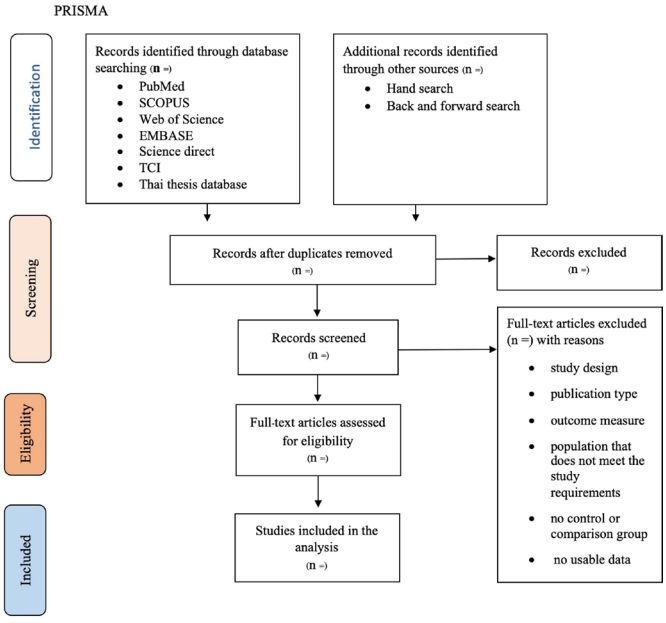

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing the study identification and selection process.

Search strategies

Seven medical databases, including PubMed, SCOPUS, Web of Science, EMBASE, ScienceDirect, Thai thesis database and TCI (Thai journals online), will be searched for studies focusing on interventions for *O. viverrini*. Electronic searches will be conducted from the inception of each database up to 13 August 2022. The searches will not be limited to any language, and in the case of languages other than English, native speakers will be consulted for full-text translations. The details of the search strategies for each database are provided in online supplemental table S2. Medical Subject Heading terms and keywords containing the name of the parasite (ie, *O. viverrini*, liver fluke), the names of the diseases caused by the parasite (eg, opisthorchiasis, CCA) and public health interventions (eg, health education, sanitation, food safety controls and mass drug administration) will be used for the search. The keywords will be combined during the search using appropriate Boolean operators. Reference lists of the included papers will be reviewed for additional studies. We will also run a backward and forward search of the included papers to check for additional studies. Corresponding authors will be contacted by email when additional information is required.

Eligibility criteria

Articles that meet the population, intervention, comparison, outcome and study design criteria will be eligible for inclusion in this systematic review (table 1).

Study selection

All articles identified in the databases will be imported to an EndNote library. After the removal of the duplicates, the articles will be exported to Rayyan for screening. The titles and abstracts of the studies will be screened independently by two investigators (MA and PS). The full-text articles will be then reviewed by the same two investigators using the predefined eligibility criteria. At this stage, the title and abstract will be reviewed, and a decision will be made as to whether an article should be included or excluded. The reasons for excluding studies include study design, publication type, outcome measure, or population that do not meet the study requirements, as well as no control or comparison group, and no usable data. Disagreement between the two reviewers will be resolved through discussion with a third reviewer (KAA).

Data extraction

Data will be extracted from eligible studies using piloted data extraction tools by the same two investigators (PS and MA) independently. The following data will be extracted: (1) first author; (2) country of the study; (3) year(s) when the study was conducted and data were collected; (4) study design; (5) population characteristics of the study (age, gender, inclusion/exclusion criteria of the participants); (6) intervention (type, duration, number of people receiving the intervention and number in the control group); and (7) number of cases, prevalence or

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Table 1 Eligibility criteria to include studies in the systematic review and meta-analysis

Eligibility criteria	Definition
Population	Adults and children screened for *Opisthorchis viverrini* infection
Intervention	Health education, sanitation, food safety controls, mass drug administration and other public health interventions
Comparison	No intervention, usual care, placebo or other preventive interventions
Outcomes	Reduction in the prevalence, incidence or number of *O. viverrini*-infected people
Study design	Randomised and non-randomised studies with either a parallel control group or historical data from the same population

incidence of *O. viverrini* at baseline and after implementation of the intervention. When multiple studies used data from the same database, the most updated and complete reports will be used to extract the data for our systematic review (online supplemental table S3).

Quality assessment

The risk of bias will be assessed by two authors independently using the Cochrane Collaboration's risk of bias tool.[12] Risks will be categorised into domains and assessed as low, high or unclear risk for each domain (online supplemental table S4).

Heterogeneity

Random-effects models will be used for conventional pairwise meta-analysis. Direct comparisons of the interventions will be evaluated by pooled relative risks (RRs) with 95% CIs and p values will be calculated using the statistical software Stata (StataCorp, College Station, Texas). Forest plots will be used to visually evaluate heterogeneity between studies. Heterogeneity will be measured quantitatively using the heterogeneity squared (I^2) index with 95% CI. The I^2 value can be interpreted as evidence of substantial levels of heterogeneity when the value is greater than 75%. Egger's regression test and funnel plot symmetry will be used to further assess the risk of publication bias.

META-ANALYSIS

The outcome measure will be the RR of *O. viverrini* infection in the intervention relative to the control groups with 95% CIs. The primary outcome will be a change in the incidence or prevalence of *O. viverrini*. A conventional meta-analysis will be first conducted for the studies to directly compare different interventions. Then, a Bayesian network meta-analysis will be conducted to undertake direct and indirect comparisons of different interventions.

Direct and indirect evidence will be summarised by a random-effects network meta-analysis model. Transitivity (ie, similarity in methodological characteristics across studies) will be explored using subgroup analyses. Consistency will be explored by examining whether indirect evidence (ie, those that are not directly compared within studies) is similar or different from direct evidence (ie, those that are directly compared within studies). We will run pairwise meta-analyses in R V.3.6.3 for direct comparisons of each outcome. The automated generalised pairwise modelling framework will be used to compare the effectiveness of different interventions (eg, education campaigns, sanitation, food safety controls and mass drug administration). Markov chain Monte Carlo methods, implemented with the WinBUGS software, will be used to calculate the pooled estimates. Further analyses will be conducted using STATA.

Meta-regression will be used to explore the source(s) of heterogeneity in intervention effects.

Patient and public involvement

This systematic review and network meta-analysis does not require patient or public involvement beyond their prior involvement in the published studies included in the review.

DISCUSSION

Various interventions have been implemented by governmental and non-governmental organisations to reduce the burden of *O. viverrini* infection in endemic countries. Integrated public health interventions have been applied in some settings to mitigate the economic burden and public health impacts of the diseases.[13–16] To our knowledge, this will be the first systematic review and network meta-analysis study to synthesise evidence on the effectiveness of public health interventions in reducing the prevalence of *O. viverrini* infection. While public health interventions have paramount importance in reducing the burden of opisthorchiasis, their comparative effectiveness in terms of reducing the prevalence or incidence of infection is yet to be investigated. Our systematic review and network meta-analysis will help identify the most effective public health intervention or combination of interventions. These findings would be crucial for both policymakers and health professionals to select the most effective interventions and scale up to regional or national levels for maximum impact.

A protocol of this systematic review is comprehensive, prospectively submitted in PROSPERO and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] In using a network meta-analysis approach, the study will be able to compare the effectiveness of different interventions without the significant costs required for comparison of multiple interventions by prospective design.

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The systematic review and network meta-analysis will be limited by the number and quality of available studies on the topic and the range of interventions tested by published studies. However, we will evaluate and assess the quality of evidence by using the Cochrane risk of bias tool and include all eligible studies.

Ethics and dissemination

Since we will use published data, formal ethical approval is unnecessary. The results of this review will be submitted to a peer-reviewed journal. Amendments of the basic protocol will be documented in the comprehensive review.

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Contributors PS, KAA, BS and ACAC developed the initial conceptualisation of this study. PS designed the search strategy. PS, KAA, ACAC, BS, ST and MA contributed to the development of the selection criteria and designing the study. KAA and ACAC assisted in statistical analysis. PS, KAA and ACAC contributed to drafting the protocol. All authors approved the final work prior to submission.

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Disclaimer The funder had no role in the design and conduct of the study; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary tables

Table S1: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Other:** primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	

From Hutton, Brian, Georgia Salanti, Deborah M. Caldwell, Anna Chaimani, Christopher H. Schmid, Chris Cameron, John P. A. Ioannidis, Sharon Straus, Kristian Thorlund, Jeroen P. Jansen, Cynthia Mulrow, Ferrán Catalá-López, Peter C. Gøtzsche, Kay Dickersin, Isabelle Boutron, Douglas G. Altman, and David Moher. "The Prisma Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions: Checklist and Explanations." *Annals of Internal Medicine* 162, no. 11 (2015/06/02 2015): 777-84. Accessed 2022/07/20. https://dx.doi.org/10.7326/M14-2385.

Supplementary tables

Table S2: Search strategies for *O. viverrini* interventions in seven different

Search	Query	Results
PubMed		
#1	¨Opisthorchiasis¨[MeSH] OR ¨Opisthorchis¨[MeSH]) OR ¨Opisthorchiasis¨ [Title/Abstract] OR ¨Opisthorchis¨ [Title/Abstract] OR ¨Liver fluke¨ [Title/Abstract]	
#2	intervention OR methods OR education OR sanitation OR latrine OR toilet OR toilet facilities OR mass-drug OR mass-drug treatment OR Anthelmintic OR praziquantel OR school OR children	
Limit to	¨Human¨	
SCOPUS		
#1	(opisthorchiasis OR opisthorchis OR liver fluke)	
#2	(Intervention OR education OR sanitation OR latrine OR mass-drug OR mass-drug treatment OR praziquantel OR school OR children)	
# 3	("epidemiology" OR "incidence" OR "prevalence" OR "risk" OR "ratio" OR "eliminate*" OR "eradicate*" OR "prevent*" OR "control*" OR "intervent*")	
# 4	# 1 AND #2 AND #3	
Limit to	Human AND English AND full article AND Opisthorchiasis	
Web of Science		
#1	Opisthorchis OR opisthorchiasis OR liver fluke	
#2	("clinical trial* " OR "randomized controlled trial*" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "cross over study*" OR "cross over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial")	
#3	#1 AND #2	
EMBASE		
#1	('opisthorchiasis'/exp OR 'opisthorchis viverrini'/exp) OR (opisthorchiasis:ab,ti OR opisthorchis:ab,ti OR 'liver fluke':ab,ti)	
#2	('intervention'/exp OR intervention':ab,ti OR health education':ab,ti OR 'sanitation':ab,ti OR 'food safety':ab,ti OR 'mass drug treatment':ab,ti OR ' anthelmintic treatment':ab,ti)	
#3	#1 AND #2	
Science Direct		
#1	Opisthorchis OR opisthorchiasis OR liver fluke OR OV OR prevalence opisthorchis	
#2	Intervention OR education OR sanitation OR latrine OR mass-drug OR mass-drug treatment OR praziquantel OR school OR children	
#3	#1 AND #2	
TCI (Thai Journal)		
#1	Opisthorchis	
#2	Opithorchiasis	
#3	Liver fluke	
#4	Intervention	
#5	#1 OR #2 OR #3 AND #4	
Thai Thesis database		
#1	Opisthorchis OR opisthorchiasis OR liver fluke	
#2	Intervention OR mass drug treatment OR sanitation OR education OR praziquantel	
#3	#1 AND #2	

Supplementary tables

Table S3: Data extraction tools

First Author	Country	Year(s)	Study design	Population characteristics					Baseline data				Post-intervention data			
				Age	Sex	Sample size	Inclusion	Exclusio	Type	Duration	No. Pop	+cases/ Prevalence	Type	Duration	No. Pop	+cases/ Prevalence

Supplementary tables

Table S4: The quality assessment tools

Bias	Authors' judgment	Support for judgment
Selection bias Random sequence generation	High Low Unclear	
Selection bias Allocation concealment	High Low Unclear	
Reporting bias Selective reporting	High Low Unclear	
Other bias Other sources of bias	High Low Unclear	
Performance bias Blinding (participants and personnel)	High Low Unclear	
Detection bias Blinding (outcome assessment)	High Low Unclear	
Attrition bias Incomplete outcome data	High Low Unclear	