

Effectiveness of the new integrated strategy to control the transmission of *Schistosoma japonicum* in China: a systematic review and meta-analysis

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Abstract – Since 2004, the national schistosomiasis control strategy in China has shifted from the morbidity control strategy (conventional strategy) to an integrated strategy (new strategy). We investigated the effectiveness of the new strategy and compared it against the conventional strategy. We retrieved from electronic databases the literature regarding the new strategy published from 2000 to 2017. The effect of the new or conventional strategy on infection by *Schistosoma japonicum* of humans and snails (*Oncomelania hupensis*) was evaluated with pooled log relative risk (logRR). A total of only eight eligible publications were included in the final meta-analysis. The results showed that implementation of the new strategy reduced the infection risk by 3–4 times relative to the conventional strategy. More specifically, the conventional strategy caused a reduction in both human (logRR = 0.56, 95% CI: 0.12–0.99) and snail infections (logRR = 0.34, 95% CI: –0.69–1.37), while the new strategy also significantly reduced both human (logRR = 1.89, 95% CI: 1.33–2.46) and snail infections (logRR = 1.61, 95% CI: 1.06–2.15). In contrast to the conventional strategy, the new strategy appeared more effective to control both human (logRR difference = 1.32, 95% CI: 0.78–1.86) and snail infections (logRR difference = 1.53, 95% CI: 0.76–2.31). Our data demonstrate that the new integrated strategy is highly effective to control the transmission of *S. japonicum* in China, and this strategy is recommended for schistosomiasis elimination in other affected regions across the world, with adaptation to local conditions.

Key words: *Schistosoma japonicum*, integrated strategy, morbidity control, effectiveness evaluation, systematic review, meta-analysis.

Résumé – Efficacité de la nouvelle stratégie intégrée de contrôle de la transmission de *Schistosoma japonicum* en Chine : revue systématique et méta-analyse. Depuis 2004, la stratégie nationale de lutte contre la schistosomiase en Chine est passée d'une stratégie de contrôle de la morbidité (stratégie conventionnelle) à une stratégie intégrée (nouvelle stratégie). Nous avons examiné l'efficacité de la nouvelle stratégie et l'avons comparée à la stratégie conventionnelle. Nous avons extrait des bases de données électroniques la littérature concernant la nouvelle stratégie publiée de 2000 à 2017. L'effet de la stratégie nouvelle ou conventionnelle sur l'infection par *Schistosoma japonicum* des humains et des mollusques (*Oncomelania hupensis*) a été évalué avec le risque relatif de log groupé (logRR). Au total, seulement 8 publications éligibles ont été incluses dans la méta-analyse finale. Les résultats ont montré que la mise en œuvre de la nouvelle stratégie réduisait de 3 à 4 fois le risque d'infection par rapport à la stratégie conventionnelle. Plus spécifiquement, la stratégie conventionnelle a entraîné une réduction des infections humaines (logRR = 0.56, IC à 95 % : 0.12–0.99) et des infections des mollusques (logRR = 0.34, IC à 95 % : –0.69–1.37), tandis que la nouvelle stratégie a aussi réduit les infections humaines (logRR = 1.89, IC à 95 % : 1.33 à 2.46) et des mollusques (logRR = 1.61, IC à 95 % : 1.06 à 2.15). Contrairement à la stratégie conventionnelle, la nouvelle stratégie a semblé plus efficace pour contrôler à la fois les infections humaines (différence de logRR = 1.32, IC à 95 % : 0.78–1.86) et les infections des mollusques (différence de logRR = 1.53, IC à 95 % : 0.76–2.31). Nos données démontrent que la nouvelle stratégie intégrée est très efficace pour contrôler la transmission de *S. japonicum* en Chine et que cette stratégie est recommandée pour l'élimination de la schistosomiase dans d'autres régions touchées du monde, avec une adaptation aux conditions locales.

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Introduction

Schistosomiasis is a parasitic disease caused by the blood flukes of the genus *Schistosoma* [8]. It ranks second after malaria among the global human parasitic diseases in terms of socio-economic and public health importance in tropical and subtropical areas [8]. Worldwide, this neglected tropical disease affects more than 207 million people in 78 countries, with 779 million people at risk of infection [37], leading to 0.2 million deaths [29] and 1.75–2.00 million disability adjusted life years (DALYs) each year [18].

Three major *Schistosoma* species are known to infect humans, including *S. haematobium*, *S. mansoni*, and *S. japonicum* [8]. Schistosomiasis japonica, caused by infection with the parasite *S. japonicum*, is endemic mainly in China, the Philippines, and parts of Indonesia [8]. Concerted control efforts since the 1950s have dramatically reduced the number of infections as well as the burden of the disease in the endemic areas of China [10, 40, 62]. However, schistosomiasis japonica remains a major public health concern in China, as one of the four priorities for communicable disease control defined by the central government [44]. Currently, the disease remains endemic in the marshland and lake regions of five provinces along the middle and lower reaches of the Yangtze River, and in some mountainous areas in the provinces of Sichuan and Yunnan, and over 0.7 million people living in China are thought to have the disease [63].

The national strategy for schistosomiasis control has shifted three times in China since it was first initiated: transmission control strategy (from mid-1950s to early 1980s), morbidity control strategy (from mid-1980s to 2003), and the new integrated strategy (2004 to present) [53, 54]. The morbidity control strategy, also known as the conventional strategy, focuses on synchronous chemotherapy for humans and bovines [4], and the new strategy developed in 2004 intervenes in the transmission pathway of schistosomiasis japonica, mainly including replacement of bovines with machines, prohibition of grazing cattle in the grasslands, improving sanitation, installation of fecal-matter containers on boats, praziquantel drug therapy, snail control, and health education [42]. This new integrated control strategy has proven to be highly effective to reducing the rate of *S. japonicum* infection in both humans and the intermediate host snails [24, 26, 39, 43, 46, 65, 66]. However, the effectiveness of this new integrated strategy varies in previous reports in terms of the implementation in different endemic regions and different local circumstances [36]. We therefore present a systematic literature review and meta-analysis to evaluate the effectiveness of the new integrated strategy to control the transmission of *S. japonicum* in China, and compare results against those of the conventional strategy.

Materials and methods

Search strategy and data source

The studies pertaining to the effectiveness of the new strategy for schistosomiasis control that were published during the period from January 1st, 2000 through December 31st, 2017, were jointly searched in electronic databases, including

PubMed, Web of Science, Embase, Proquest, Cochrane Library, China National Knowledge Infrastructure (CNKI), the Wanfang Database and VIP Database. The terms we used included “schistosomiasis”, in combination with “integrated control strategy”, “comprehensive control strategy” or “infectious source control measures”. The title and abstract of each publication screened were read carefully, and the full texts were reviewed.

Study selection

Both inclusion and exclusion criteria were defined for identifying the publications included in our meta-analysis. Inclusion criteria involved: (1) the control measures targeting schistosomiasis japonica; (2) the implementation of the study in China; (3) a detailed description of integrated control interventions with emphasis on control of infectious source of schistosomiasis; (4) inclusion of both study and control areas, and assessment of effectiveness in both groups; (5) a description and evaluation of prevalence of human *S. japonicum* infection and snail infection as outcomes of the interventions; and (6) available full text for review. The literature articles that met the following criteria were excluded: (1) lack of control areas or lack of effectiveness evaluation in control areas; (2) no description of quantitative outcomes of interventions; (3) the original data regarding the outcomes of interventions were not available; and (4) the full text was unavailable.

Assessment of publication bias

A funnel plot was drawn to evaluate literature quality. We tested funnel plot asymmetry based on the linear regression method [38] using the metabias function in the meta package of R software [34]. We used a cut-off *p*-value of <0.05 to determine the asymmetry of the funnel plot, and further the presence of publication bias.

Meta-analysis

We carried out a meta-analysis (fixed- or random-effects models) using the RMA function in the metafor package of R software [41]. The effects of the new or conventional strategy in human/snail studies were evaluated with pooled log relative risk (logRR) and the corresponding 95% confidential interval (CI). We then calculated the logRR difference between the strategies and the standard error (*SE*) as below:

$$\begin{aligned} \log RR \text{ difference} &= \log RR \text{ new strategy} \\ &\quad - \log RR \text{ conventional strategy,} \end{aligned}$$

$$SE(\log RR \text{ difference}) =$$

$$\sqrt{SE(\log RR \text{ new strategy})^2 + SE(\log RR \text{ conventional strategy})^2},$$

from which we further compared the two strategies with pooled logRR differences. In all analyses, Cochran's *Q* test and *I*² statistics were employed to measure the heterogeneity between studies. A random effects model was employed to

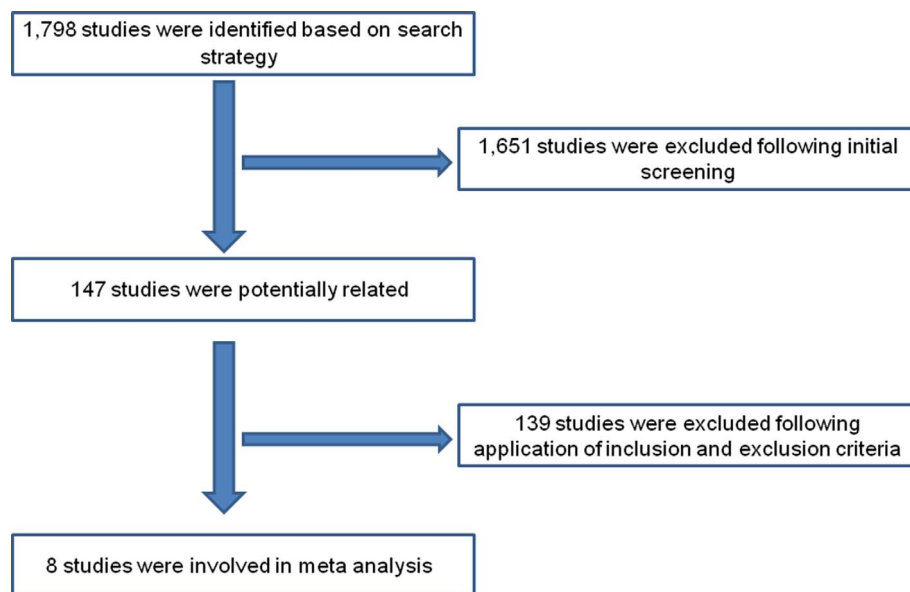


Figure 1. Flowchart of study selection.

estimate overall studies if heterogeneity existed in the data source. Otherwise, a fixed-effect model was reported.

All statistical analyses were performed using *R* software, and a *p*-value of <0.05 was considered statistically significant.

Results

Literature searched

A total of 1798 publications were identified, of which 147 articles were potentially relevant according to the initial screening. Following the application of the inclusion and exclusion criteria, 139 studies were excluded. Finally, eight papers that examined the effectiveness of the new strategy were included in the meta-analysis (Fig. 1), of which five included two study areas and two control areas. Table 1 describes the general characteristics of the studies enrolled in the analysis [15, 25, 27, 42, 43, 59–61].

Literature quality

We evaluated the quality of the articles included in this study according to the funnel plot asymmetry using metabias function in the *R* package meta. Symmetry of the funnel plot was observed, with all *p* values of >0.05 (Fig. 2). The results indicated no publication bias present in the articles used in the meta-analysis.

Meta-analysis

A heterogeneity test revealed the presence of heterogeneity among studies that reported the effect of the conventional strategy on the control of human *S. japonicum* infection ($I^2 = 90.34$, $p < 0.001$) and snail infection ($I^2 = 83.52$, $p < 0.001$), and the new integrated strategy on the control of human infection ($I^2 = 86.39$, $p < 0.001$). No heterogeneity

was detected among the studies reporting the alteration of snail infection caused by the new strategy ($I^2 = 0.92$, $p = 0.361$). We then estimated pooled logRR and the corresponding 95% CI using random and fixed effects models, respectively.

We found that the implementation of the conventional strategy caused a reduction in both human *S. japonicum* (logRR = 0.56, 95% CI: 0.12–0.99; Fig. 3A) and snail infections (logRR = 0.34, 95% CI: –0.69–1.37; Fig. 3B), while the new strategy significantly reduced both human *S. japonicum* (logRR = 1.89, 95% CI: 1.33–2.46; Fig. 4A) and snail infections (logRR = 1.61, 95% CI: 1.06–2.15; Fig. 4B). In other words, the conventional strategy reduced the risk of infection by 1.75-fold (95% CI: 1.13–2.69 fold) in humans and 1.4-fold (95% CI: 0.5–3.94 fold) in snails, while the new strategy reduced 6.62-fold (95% CI: 3.78–11.7 fold) the risk of infection in humans and 5-fold (95% CI: 2.89–8.58 fold) in snails. Further comparison between these two strategies indicated that the new strategy was 3.74-fold (95% CI: 2.18–6.42) (logRR difference = 1.32, 95% CI: 0.78–1.86; Fig. 5A) more effective in human infection control and 4.62-fold (95% CI: 2.14–10.07) (logRR difference = 1.53, 95% CI: 0.76–2.31; Fig. 5B) more effective in snail infection control as compared to the conventional strategy.

Discussion

The description of schistosomiasis in China dates back more than two millennia [64]. Historically, this parasitic disease was called the “god of plagues” by Chairman Mao, the founder of the People’s Republic of China [2, 3]. The disease has caused high social and economic burdens because of its very high rates of morbidity and mortality [56].

The Chinese national schistosomiasis control program was launched in the mid-1950s, and has had three different stages: transmission control strategy, morbidity control strategy, and integrated strategy [53, 54]. In the first stage (from

Table 1. Characteristics of the studies included in the meta-analysis

No.	Study region	Study period	Integrated interventions targeting control of infectious sources	Study measurements	References
1	Anhui province	2002–2003	Replacement of cattle with machines, improvement of sanitation, and building lavatories and latrines	Human <i>S. japonicum</i> infection and snail infection	[61]
2	Mountainous regions of Yunnan province	2006–2007	Improvement of sanitation, and building lavatories and latrines and prohibition of grazing cattle in the grasslands	Human <i>S. japonicum</i> infection and snail infection	[27]
3	Poyang Lake region	2005–2007	Removing cattle from snail-infested grasslands, providing farmers with mechanized farm equipment, improving sanitation by supplying tap water and building lavatories and latrines, providing boats with fecal matter containers, and implementing an intensive health education program	Human <i>S. japonicum</i> infection and snail infection	[42]
4	Four provinces of Anhui, Hubei, Hunan and Jiangxi	2005–2008	Removing cattle from snail-infested grasslands, providing farmers with mechanized farm equipment, improving sanitation by supplying tap water and building lavatories and latrines, providing boats with fecal matter containers, and implementing an intensive health education program	Human <i>S. japonicum</i> infection and snail infection	[43]
5	Xuancheng city of Anhui province	2006–2007	Replacement of cattle with machines, improvement of sanitation, and building lavatories and latrines	Human <i>S. japonicum</i> infection and snail infection	[59]
6	Jingzhou city of Hubei province	2010–2011	Replacement of cattle with machines, and prohibition of grazing cattle in the grasslands	Human <i>S. japonicum</i> infection and snail infection	[25]
7	Gong'an county of Hubei province	2009–2011	Building fences to limit the grazing area for cattle, building safe pastures for grazing, improving the residents' health conditions and facilities	Human <i>S. japonicum</i> infection and snail infection	[15]
8	Jinxian county along Poyang Lake region	2004–2005	Grazing and marshland isolation, replacing cattle with tractors, and improving access to water and sanitation facilities	Human <i>S. japonicum</i> infection and snail infection	[60]

mid-1950s to early 1980s), a transmission control strategy was implemented with emphasis on the control of the intermediate host snails, and mass campaigns were launched to eliminate snail hosts by environmental modification and mollusciciding [13]. During this period, snail habitats were greatly reduced, and the number of schistosomiasis cases decreased [45]. The national schistosomiasis control strategy shifted to morbidity control (from the mid-1980s to 2003) as a response to the advent of the highly effective and low-cost schistosomicide praziquantel [1, 5, 47, 51]. During this stage, five out of the

12 provinces that were endemic for the parasite achieved transmission interruption of schistosomiasis [48]. However, the termination of the World Bank Loan Project for Schistosomiasis Control in 2001 [50] and frequent flooding along the Yangtze River basin [49] resulted in a resurgence of schistosomiasis japonica in China [21, 42, 43]. In order to consolidate the achievements attained and to eliminate schistosomiasis in the country, the Chinese government reinforced the national schistosomiasis control program and prioritized schistosomiasis, together with HIV/AIDS, hepatitis B and tuberculosis in

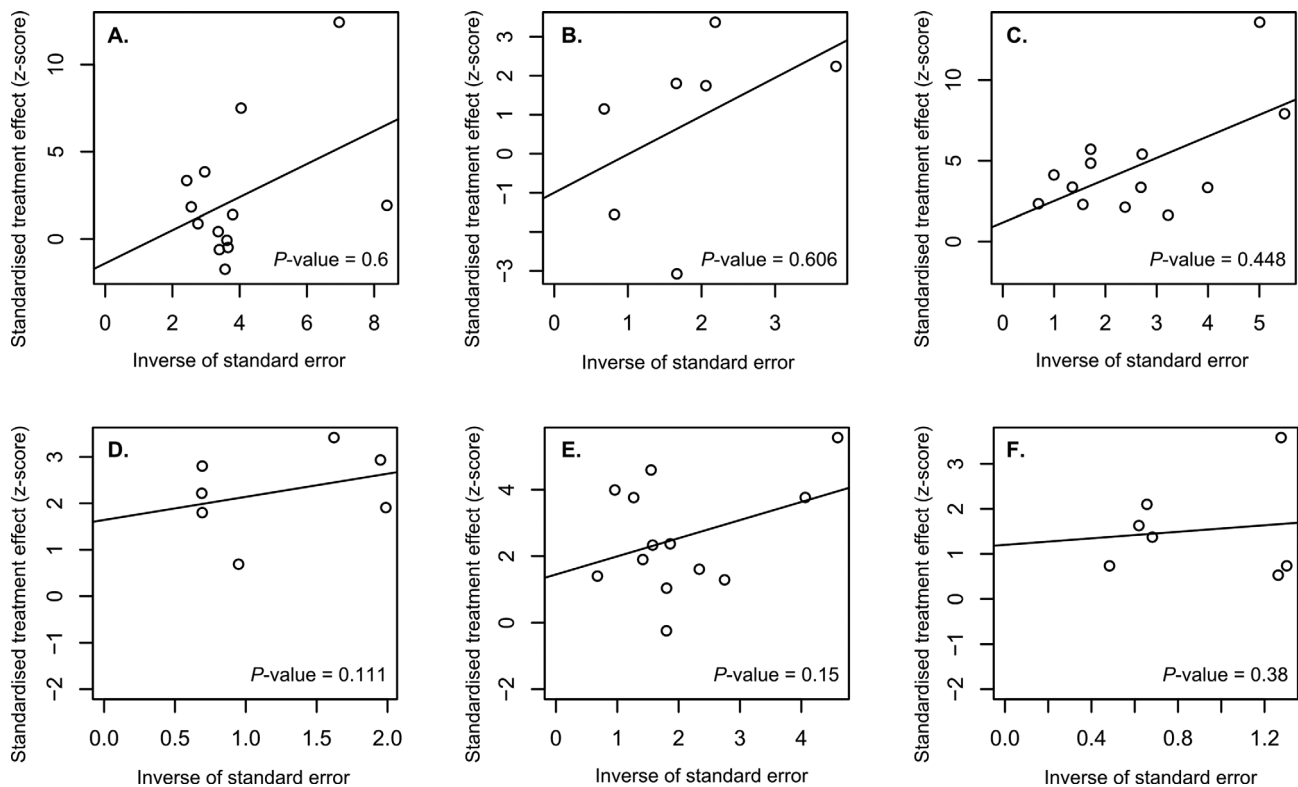


Figure 2. Funnel plot shows asymmetry for the studies included in this analysis. (A) the funnel plot of the studies reporting the effectiveness of the conventional strategy on the control of human *Schistosoma japonicum* infection; (B) the funnel plot of the studies reporting the effectiveness of the conventional strategy on the control of *Oncomelania hupensis* snail infection; (C) the funnel plot of the studies reporting the effectiveness of the new strategy on the control of human *Schistosoma japonicum* infection; (D) the funnel plot of the studies reporting the effectiveness of the new strategy on the control of *Oncomelania hupensis* snail infection; (E) the funnel plot of the studies comparing the effectiveness between the new strategy and the conventional strategy on the control of human *Schistosoma japonicum* infection; (F) the funnel plot of the studies comparing the effectiveness between the new strategy and the conventional strategy on the control of *Oncomelania hupensis* snail infection.

communicable disease control [44]. In addition, a new integrated strategy targeting the transmission pathway of schistosomiasis japonica was proposed to stop environmental contamination with schistosome eggs, which emphasizes replacement of cattle with machines, improvements in sanitation, and fencing of water buffaloes, along with health education, praziquantel-based drug therapy and snail control [42].

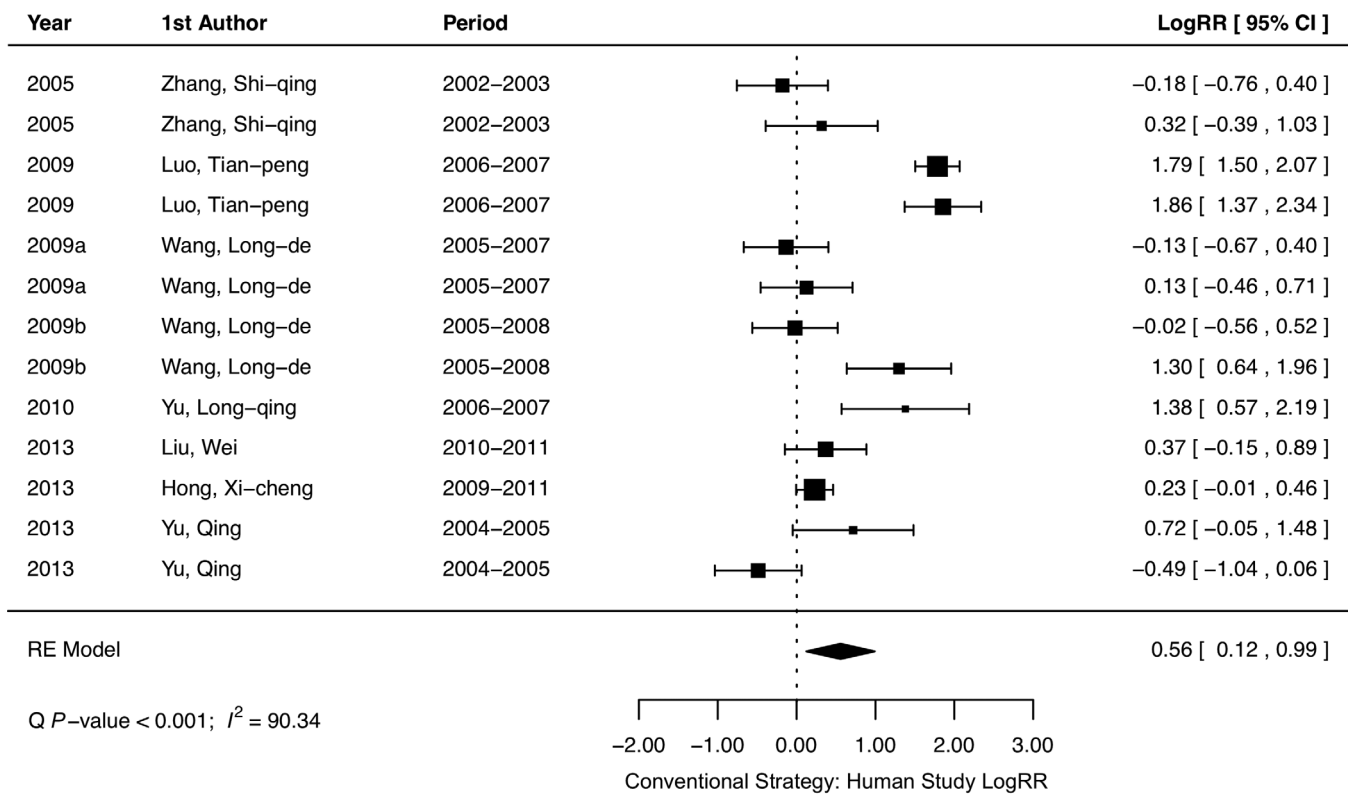
The new integrated strategy was designed to reduce the role of cattle and humans as sources of *S. japonicum* infection [42]. It has been highly effective in controlling the transmission of *S. japonicum* in the endemic foci of China [6, 11, 14, 20, 58, 65]. Since the new strategy was implemented in various endemic regions and different combinations of interventions were adopted, the effectiveness of the strategy in reducing infection by *S. japonicum* in humans and the intermediate host snails has been found to vary in previous studies. However, there has been no systematic evaluation of this new strategy to control the transmission of *S. japonicum* in China until now. We therefore carried out a systematic literature review and meta-analysis with the aim of performing a pooled analysis of the effectiveness of the new strategy, and comparing the effectiveness of the new strategy with the

conventional strategy in reducing *S. japonicum* infection in both humans and snails.

Our meta-analysis showed that the implementation of the conventional strategy caused a reduction in both human *S. japonicum* infection (logRR = 0.56, 95% CI: 0.12–0.99) and snail infection (logRR = 0.34, 95% CI: –0.69–1.37), suggesting that the praziquantel-based morbidity control strategy is effective in reducing *S. japonicum* infection in humans and snails, while the new strategy remarkably reduced both human *S. japonicum* (logRR = 1.89, 95% CI: 1.33–2.46) and snail infections (logRR = 1.61, 95% CI: 1.06–2.15), indicating that the integrated strategy with emphasis on controlling the source of *S. japonicum* infection is effective in controlling the transmission of *S. japonicum*. However, the new strategy appeared more effective in controlling both human *S. japonicum* (logRR difference = 1.32, 95% CI: 0.78–1.86) and snail infections (logRR difference = 1.53, 95% CI: 0.76–2.31) than the conventional strategy.

The morbidity control strategy mainly involves praziquantel-based drug therapy, snail control, and health education interventions [28]. Nevertheless, praziquantel is ineffective in preventing *S. japonicum* infection and re-infection [23], and

A. Effect of conventional strategy on human infection



B. Effect of conventional strategy on snail infection

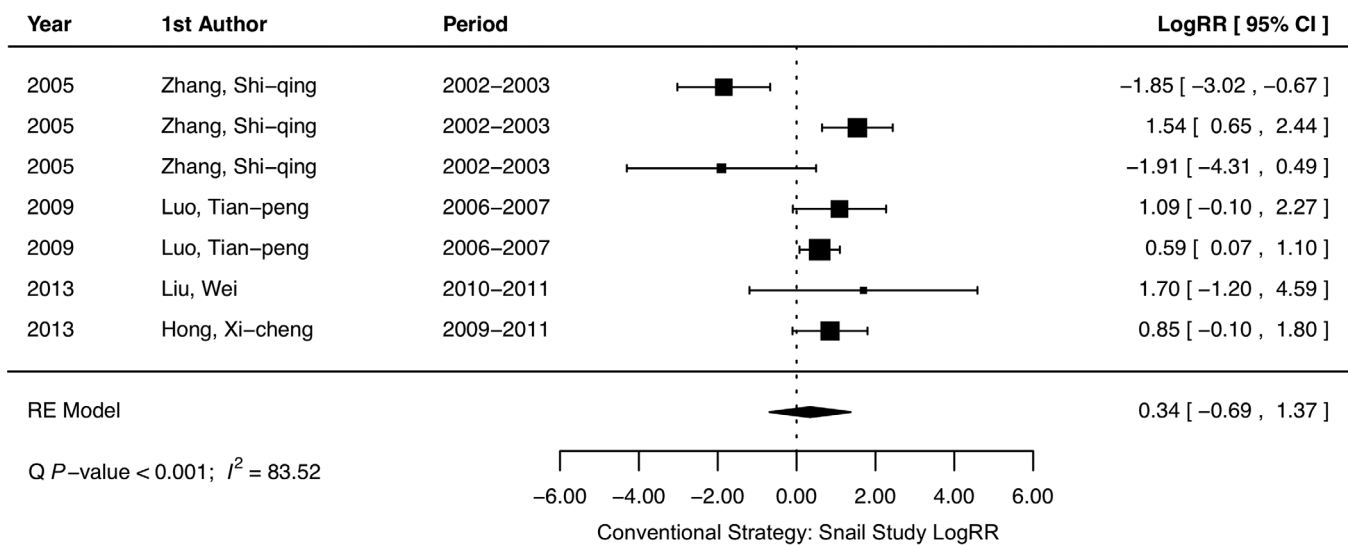


Figure 3. Effectiveness of the conventional strategy on the control of human *Schistosoma japonicum* infection (A) and *Oncomelania hupensis* snail infection (B).

it is unlikely to eliminate snails completely in the endemic foci [62]. China's experiences and lessons from the past three decades of schistosomiasis control have shown that the morbidity control strategy is insufficient to eliminate schistosomiasis in the country [62, 67]. In the Philippines, mass drug administration with praziquantel on its own has

proven to be ineffective to control the prevalence of schistosomiasis, the intensity of *S. japonicum* infection, or the morbidity of the disease [17, 31, 32]. Moreover, praziquantel-based deworming alone has been proved ineffective to eliminate schistosomiasis from the African mainland [7, 9, 16, 35]. These findings demonstrate that the sustainable control and

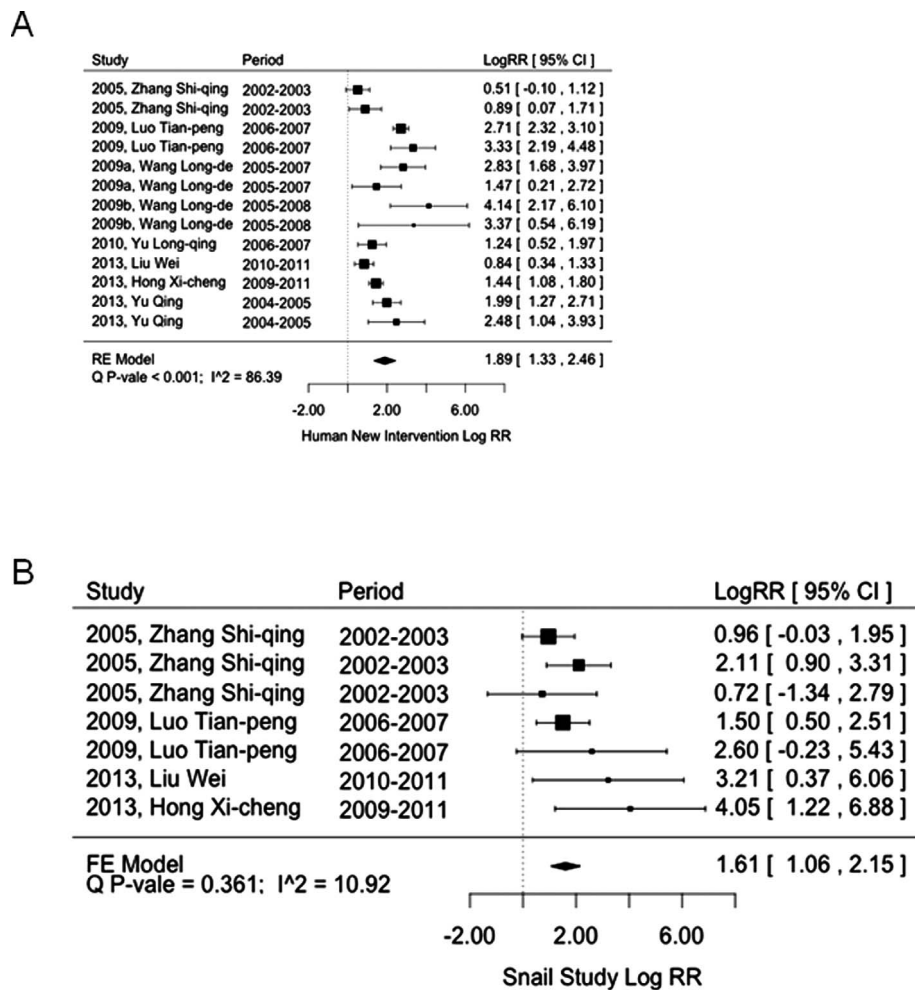


Figure 4. Effectiveness of the new strategy on the control of human *Schistosoma japonicum* infection (A) and *Oncomelania hupensis* snail infection (B).

elimination of schistosomiasis requires an integrated, multidisciplinary and multi-component strategy [30].

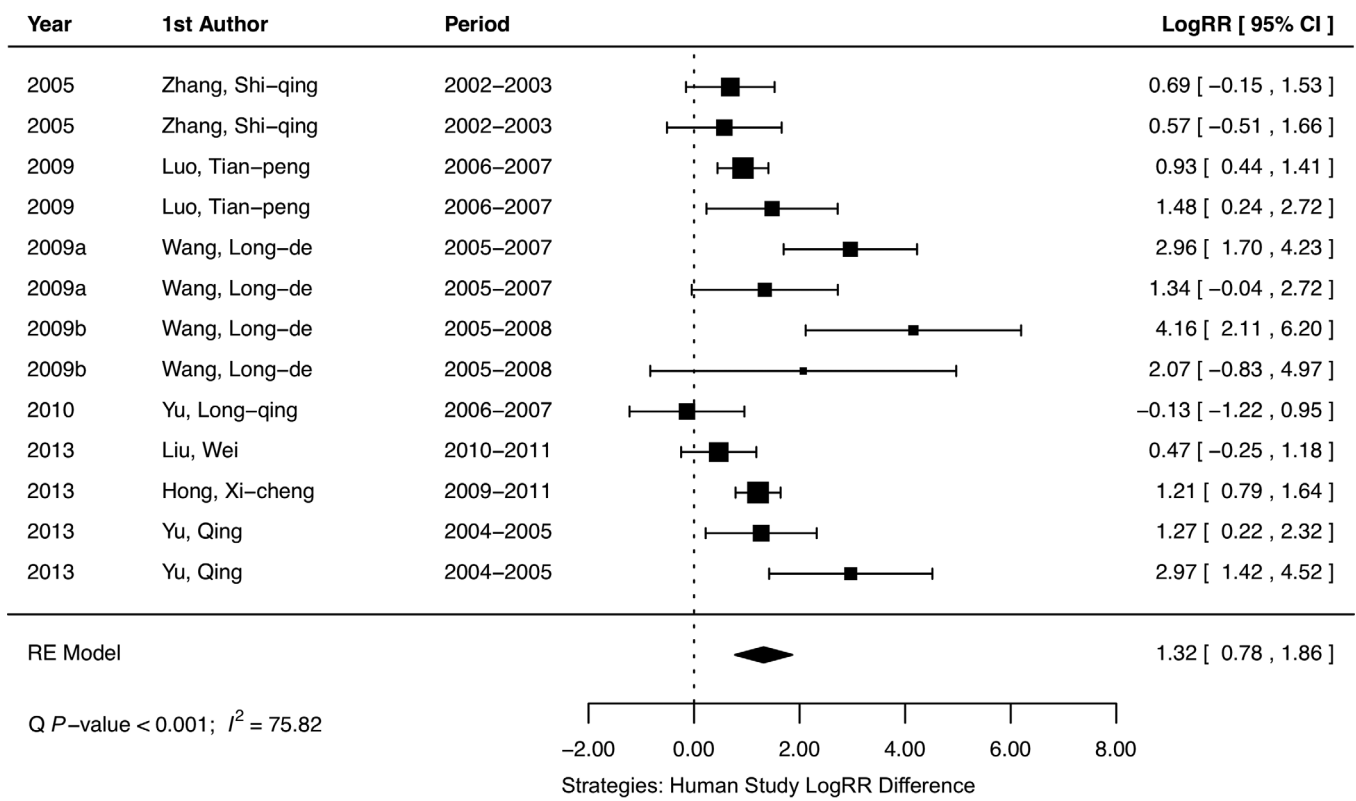
The integrated strategy relies on the fact that cattle have been considered as the major infectious source for the transmission of schistosomiasis in the marshland and lake regions of China [12, 22]. It is therefore assumed that the successful intervention packages piloted in the marshland and lake regions are not fully suitable for the hilly and mountainous environments in the Sichuan and Yunnan provinces of China [36]. Although field studies have shown that this new integrated strategy remains effective to control *S. japonicum* infection in humans and snails in hilly and mountainous endemic foci [26, 27, 57], regionally flexible integrated, intersectoral, and setting-specific control strategies driven by local circumstances and data are needed [36].

The present study has some limitations. First, only eight eligible studies were enrolled in the meta-analysis. A total of 147 potentially relevant literatures were initially identified; however, 139 studies were excluded due to unavailability of original data regarding *S. japonicum* infection in humans and snails in the articles. In addition, most of the studies were published in national journals. Therefore, more randomized controlled trials with a rigorous design to evaluate the effect

of the integrated control strategy for schistosomiasis japonica seem justified, and the research outcomes are encouraged to be transferred around the world. Second, no stratified analysis was performed. Since there were only eight studies included in the meta-analysis, we evaluated the effectiveness of the new integrated strategy implemented in endemic foci with various endemic types, and did not assess the endemic type-specific effectiveness. Further systematic evaluations recruiting more trials to evaluate the effectiveness of the new integrated strategy for controlling the transmission of *S. japonicum* in the marshland and lake regions, the mountainous regions and plain regions, respectively, seem justified.

In summary, the results of the present study demonstrate that the new integrated strategy with emphasis on the control of the infectious source is highly effective to control the transmission of *S. japonicum* in China. The elimination of schistosomiasis japonica in the country requires continually effective and extensive implementation of an integrated, intersectoral, and setting-specific control strategy. Currently, China is transferring its expertise in schistosomiasis control to Africa, and the Philippines may also learn much from China's experiences and lessons [52, 55]. Experiences and lessons from China are important for shaping the schistosomiasis

A. Compare effects of two strategies on human infection



B. Compare effects of two strategies on snail infection

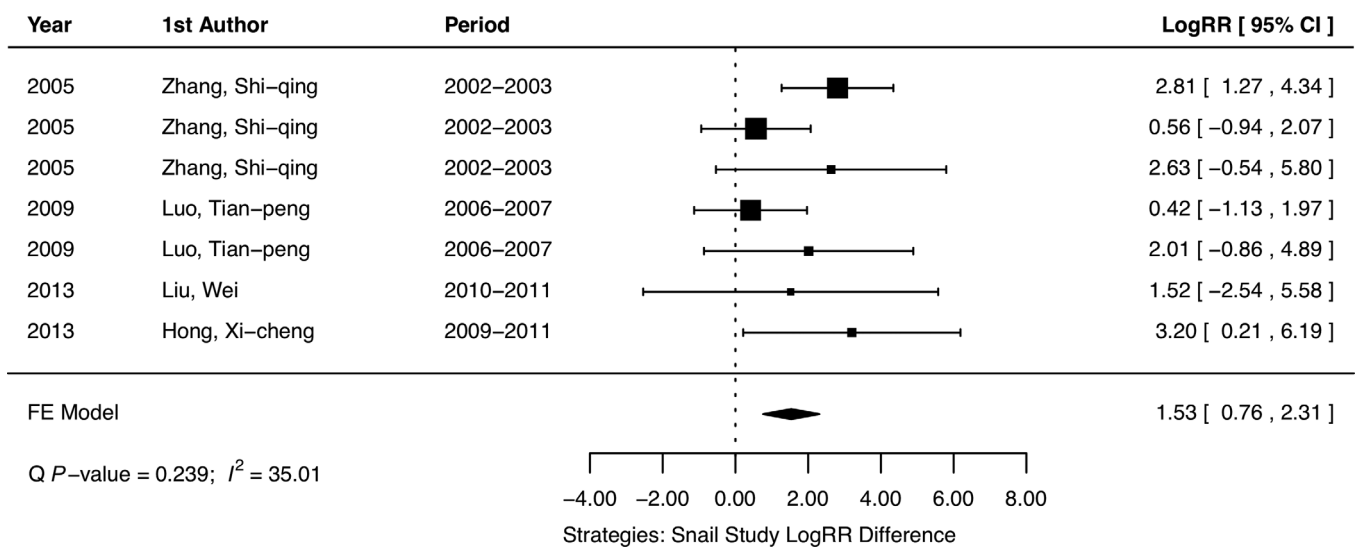


Figure 5. Comparison of the conventional strategy versus the new strategy on the control of human *Schistosoma japonicum* infection (A) and *Oncomelania hupensis* snail infection (B).

elimination agenda [19]. However, there is still a need to devise an optimal control strategy with adaptation to local circumstances to facilitate the progress towards the elimination of schistosomiasis in Africa and the Philippines [33].

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