2023

First Bovine Vaccine to Prevent Human Schistosomiasis - A Cluster Randomised Phase 3 Clinical Trial

Allen G. Ross

Donald A. Harn

Delia Chy

Marianette Inobaya

Jerric R. Guevarra

See next page for additional authors

Original Publication Citation

Ross, A. G., Harn, D. A., Chy, D., Inobaya, M., Guevarra, J. R., Shollenberger, L., Li, Y., McManus, D. P., Gray, D. J., & Williams, G. M. (2023). First bovine vaccine to prevent human schistosomiasis - a cluster randomised Phase 3 clinical trial. *International Journal of Infectious Diseases*, *129*, 110-117. https://doi.org/10.1016/j.ijid.2023.01.037

International Journal of Infectious Diseases 129 (2023) 110–117

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

First bovine vaccine to prevent human schistosomiasis - a cluster randomised Phase 3 clinical trial

Allen G. Ross[1,*], Donald A. Harn[2], Delia Chy[3], Marianette Inobaya[4], Jerric R. Guevarra[4], Lisa Shollenberger[5], Yuesheng Li[6], Donald P. McManus[6], Darren J. Gray[7], Gail M. Williams[8]

[1] *Rural Health Research Institute, Charles Sturt University, Orange, NSW, Australia*
[2] *Department of Infectious Diseases, College of Veterinary Medicine and Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, USA*
[3] *Municipal Officer of Health, Palapag, Northern Samar, The Philippines*
[4] *Research Institute for Tropical Medicine, Manila, The Philippines*
[5] *Department of Biological Sciences, Old Dominion University, Norfolk, Virginia, USA*
[6] *Infectious Diseases Division, QIMR Berghofer Medical Research Institute, Brisbane, Australia*
[7] *Research School of Population Health, Australian National University, Canberra, Australia*
[8] *School of Public Health, University of Queensland, Brisbane, Australia*

ARTICLE INFO

Article history:
Received 7 October 2022
Revised 13 January 2023
Accepted 25 January 2023

Keywords:
Schistosomiasis
Zoonosis
Bovines
Vaccination
Control
One Health

ABSTRACT

Objective: Schistosomiasis is a neglected tropical parasitic disease caused by blood flukes of the genus *Schistosoma*. *Schistosoma japonicum* is zoonotic in China, the Philippines, and Indonesia, with bovines acting as major reservoirs of human infection. The primary objective of the trial was to examine the impact of a combination of human mass chemotherapy, snail control through molluscicide, and SjCTPI bovine vaccination on the rate of human infection.

Methods: A 5-year phase IIIa cluster randomized control trial was conducted among 18 schistosomiasis-endemic villages comprising 18,221 residents in Northern Samar, The Philippines.

Results: Overall, bovine vaccination resulted in a statistically significant decrease in human infection (relative risk [RR] = 0.75; 95% confidence interval [CI] = 0.69 to 0.82) across all trial follow-ups. The best outcome of the trial was when bovine vaccination was combined with snail molluscicide. This combination resulted in a 31% reduction (RR = 0.69; 95% CI = 0.61 to 0.78) in human infection.

Conclusion: This is the first trial to demonstrate the effectiveness of a bovine vaccine for schistosomiasis in reducing human schistosome infection. The trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN12619001048178).

Introduction

Schistosomiasis is a neglected tropical parasitic disease caused by blood flukes of the genus *Schistosoma*. Globally, it ranks third among the most devastating tropical diseases and is a major cause of morbidity in Asia, Africa, South America, the Middle East, and the Caribbean [1,2]. Praziquantel (PZQ), a pyrazinoisoquinoline derivative, is the mainstay of treatment and a critical part of community-based schistosomiasis control programs [2–6]. There is currently no commercially available human vaccine against any of the human schistosomes.

Schistosomiasis japonica was first reported in the Philippines in 1906 [7]. Approximately 80% of the burden of disease now resides on the islands of Samar, Leyte, and Mindanao. An estimated 29 million people live in these three endemic zones [8–10]. Recent reports have found prevalence rates ranging from 0.7-47% for Western Samar, 5-46% for Northern Samar, and 25-60% for Leyte [8]. The current national control program comprises annual free mass drug administration with 40 mg/kg of PZQ in all schistosomiasis-endemic communities with a prevalence of >10%.

In the study area of Laoang and Palapag in Northern Samar, an active schistosomiasis control program has been ongoing since

* Corresponding author.
E-mail address: agpross@csu.edu.au (A.G. Ross).

https://doi.org/10.1016/j.ijid.2023.01.037

1980 by the local Department of Health. From 1980 to 1990, the program consisted of active case finding and directly observed therapy (DOT) of all positive cases with 60 mg/kg of PZQ. Samples were obtained from approximately 10–20% of the target population aged 5-65 years. From 1990 to 2007, case finding was intensified to include approximately 30-50% of the entire schistosomiasis-endemic population. All stool-positive individuals again received DOT with 60 mg/kg of PZQ. There is presently intermittent mass drug administration (MDA) done by the National Department of Health in known highly endemic areas [7–10].

Schistosomiasis control in China and the Philippines is complicated by the zoonotic nature of the disease, with bovines (water buffaloes and cattle) acting as major reservoir hosts [8,11–14]. Alternative sustainable control strategies are required to combat schistosomiasis to overcome rapid reinfection, the potential threat of PZQ resistance, and problems of drug compliance currently only at levels of 25-40% in China and the Philippines [15–23]. A multifaceted integrated approach targeting transmission pathways for the disease could comprise complementing PZQ treatment with vaccination of bovines and snail control as the key to sustainable control and eventual elimination (defined as the reduction to zero in human incidence) [10–14]. In light of their importance as major reservoirs for *S. japonicum*, vaccination of bovines has been proposed as a tool to assist in long-term prevention, which is supported by mathematical modeling [10–14]. The intervention would be particularly applicable to areas where mechanized farming is unsuitable. Vaccination can reduce egg excretion from cattle and buffalo, thereby interrupting transmission from bovines to snails. We previously showed that a schistosome plasmid DNA vaccine (SjCTPI-Hsp70) induced very good efficacy against *S. japonicum* in Chinese water buffaloes when it was co-administered with an IL-12 expressing plasmid as adjuvant [24,25].

We report here the results of a 5-year phase IIIa cluster randomized control trial (RCT) using a multi-factorial design in Northern Samar, The Philippines. The trial aimed to determine the impact of a combination of human mass chemotherapy, snail control through molluscicide, and the SjCTPI bovine vaccine, on the human incidence of *S. japonicum*.

Methods

Study design and randomization

Ethical consent for the trial was obtained from the human and animal ethical review boards of the National Department of Health in the Philippines (Institutional Review Board # 2012-13-0) and Griffith University (PBH/24/11/HREC0), Australia. The Research Institute for Tropical Medicine monitored the trial. Written informed consent was obtained from each individual, or, for those aged <15 years, from their parents/legal guardians before commencing the study. The phase IIIa clustered RCT used a split-plot design with the main plots being the factor designating the non-vaccine intervention groups (i.e., control, human MDA, or molluscicide) (Supplement 1). The 18 selected villages were arranged in pairs, within which villages were matched on baseline-assessed factors, which included human and bovine population numbers and prevalence, and factors affecting schistosomiasis transmission: numbers of snail colonies, type of snail habitat, water source, and distance to a health center. The nine sets of paired villages were then each randomly allocated to one of the three non-vaccine intervention groups, resulting in three pairs for each. Villages within each matched pair were allocated to one of two letter-codes for the vaccine/placebo intervention. The investigators, including the research team and study participants, were blind to the vaccine allocation to the letter code.

Participants

We commenced the phase IIIa clustered RCT with a cross-sectional parasitological survey in July to October 2012 among 22 schistosomiasis-endemic barangays in the municipalities of Laoang and Palapag in Northern Samar, the Philippines (Figure 1) [26]. The baseline survey comprised 18,221 eligible residents (age range, 5-65 years). In brief, the baseline survey included (i) A medical questionnaire that comprised information on their demographic characteristics (name, age, sex, level of education, and occupation), schistosome exposure (place, frequency, and duration), treatment history (diagnosis, number of times treated, and participation in the MDA program in the past 5 years), and level of morbidity (fever, diarrhea, abdominal pain, malaise, hepatitis status, and alcohol intake); (ii) The head of each household completed a questionnaire that included information on home and land ownerships, number of animals owned and raising practices, animal waste disposal practices, pasturing of animals, sanitation, and housing characteristics (roof, wall, and floor materials); (iii) Collection of a human stool sample, which was tested for *S. japonicum* infection using the Kato Katz (KK) thick smear technique (three smears per stool) and to determine the infection intensity (Geometric Mean Eggs per Gram [GMEPG]) [26]; (iv) Collection of bovine stool samples, which were tested for *S. japonicum* infection using the formalin-ethyl acetate sedimentation-digestion (FEA-SD) [12] and to determine infection intensity; (v) Oncomelania snail surveys using the Chinese method of random quadrat sampling applied to marshland areas for each village [10]; and (vi) An ultrasonography study conducted on a subsample of patients who either reported symptoms of gastrointestinal illness or were believed to have clinical morbidity, based on physical examination [26].

Interventions

Following the baseline survey, the interventions were implemented in 18 villages from 2013 to 2017 (Supplement 2). All stool-positive residents (60 mg/kg split DOT dose) and bovines (30 mg/kg) were treated with PZQ in the 18 study villages. Interventions were then implemented in the allocated villages as described previously. Bovines received the priming SjCTPI DNA vaccine in 2012 and then the protein boost or placebo control in VacSIM 6 months later, in 2013, with subsequent booster vaccinations or placebo controls in VacSIM given in 2014, 2015, and 2016 (Supplement 2). Full details of the production and formulation of the SjCTPI vaccines (plasmids encoding SjCTPI-HSP70 and UMVC3-mIL12 and recombinant SjCTPI), placebo control vaccine, the vaccination regimen, and the procedures for injecting bovines with the vaccine/placebo formulations have been provided [24]. VacSIM was previously described [25]. Briefly, buffalo were primed with GLP grade plasmid DNAs (SjCTPI and IL-12, 300ug of each) by intramuscular injection into the shoulder. Controls received naked plasmid DNA plus interleukin (IL)-12 plasmid DNA. Approximately 6 months post-prime, bovines were boosted by intramuscular injection of 100ug of GLP grade recombinant SjCTPI in 1.0% VacSIM containing 100ugs Bovine CpGs (Bovine ODN 2007). Controls were given CpGs in saline in 1.0% VacSIM®. Human mass treatment with 40 mg/kg of PZQ was carried out annually in the treatment arms. Molluscicide was conducted after the annual snail surveys. Targeted snail 'hotspots' (areas close to human habitation with maximum or daily access to both humans and bovines in an environment favored by snails) were sprayed with niclosamide (2 g/m^2) annually [26]. One of the villages allocated to molluscicide could not be treated for security reasons, so one of the other 18 villages, originally not selected to receive molluscicide, was selected.

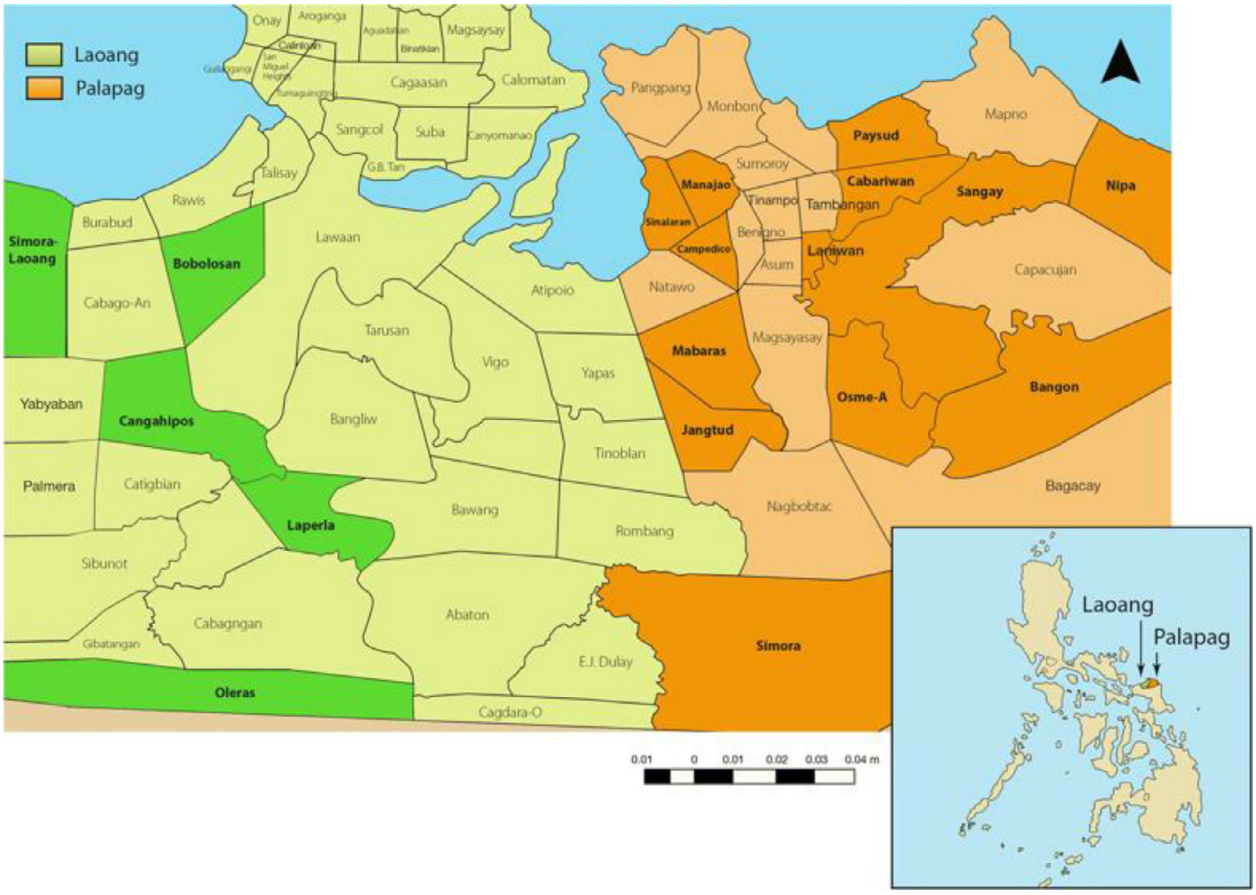

Figure 1. Map of the Philippines showing the municipalities of Palapag and Laoang in Northern Samar with the 18 study barangays highlighted.

Outcomes

The primary outcome was human *S. japonicum* infection status at two follow-ups in 2014/2015 and 2016/2017, with a positive infection defined as the presence of at least one egg on a KK slide. The secondary outcome was a human geometric mean intensity of infection in positives, as determined by the KK method.

Statistical analysis

All data management and analyses used SAS (r) Proprietary Software 9.4 (TS1M2) (2002-2012, SAS Institute Inc., Cary, North Carolina, USA, Licensed to University of Queensland - EAS, Site 10005036). Data were double-entered into a specially designed Microsoft Access-based database we developed; electronic copies of all entered data were saved offline, and backup paper duplicates were stored in a secure location [23,26]. Questionnaire survey data and results of the stool examinations were collected during the baseline survey from 2012 to 2013 and at follow-ups from 2014 to 2017 (Figure 2). Baseline and follow-up data for each village were cleaned and combined for the analyses in this paper. Based on intervention efficacy estimations (bovine vaccine efficacy 50%, human chemotherapy efficacy 85%, and targeted molluscicidding predicted efficacy 75%), an average infection rate of 10% in non-intervention villages, and a design effect (relating to paired differences) of 1.5, the study was proposed to have at least 90% power to detect the intervention effects [19,23]. A SAS program was written to carry out the randomization of each intervention group [19–23].

Analyses of human infection were restricted to those who satisfied the initial inclusion criteria (e.g., age, current residency, expected residency during the trial) and had baseline questionnaire and stool results and at least one follow-up stool result. Interventions were analyzed as intention-to-treat; i.e., the two villages not treated according to their original allocation to molluscicidding were assigned their original allocation for the purpose of analysis. Baseline infection prevalence and intensity were compared across intervention groups using logistic regression and normal regression (log-transformed EPG in those infected), respectively, with account taken of cluster effects within villages.

For intervention assessment, the primary outcome was human *S. japonicum* infection status at two follow-ups in 2014/2015 and 2016/2017, with a positive infection defined as the presence of at least one egg on a KK slide [26]. The intervention analysis used a random effects model with village pairs as a random factor. The main plot factor (control, human treatment, molluscicidding) and the vaccine allocation were treated as separate 3-level and 2-level factors, respectively. A Poisson/log link model was used with robust variances specified, as described by Zou and Donner [27], thus yielding relative risks with appropriate standard errors as effect estimates. Using Proc GLIMMIX in SAS 9.4, a full factorial model was first fitted, including a factor for time (baseline, follow-ups one and two), with baseline infection status, sex, and age group as covariates. The GLIMMIX specification incorporated three RANDOM statements, one specifying the use of an over-dispersion factor to obtain robust estimates of variance, one specifying the split-plot design with village pair as a random factor, and one specifying the repeated measures within individuals over time. The complete factorial model involves a third-order interaction (main plot x vaccine x time), which was clearly non-significant ($P = 0.99$) and was removed from the model. The second-order interaction between the main plot factor and the vaccine was retained.

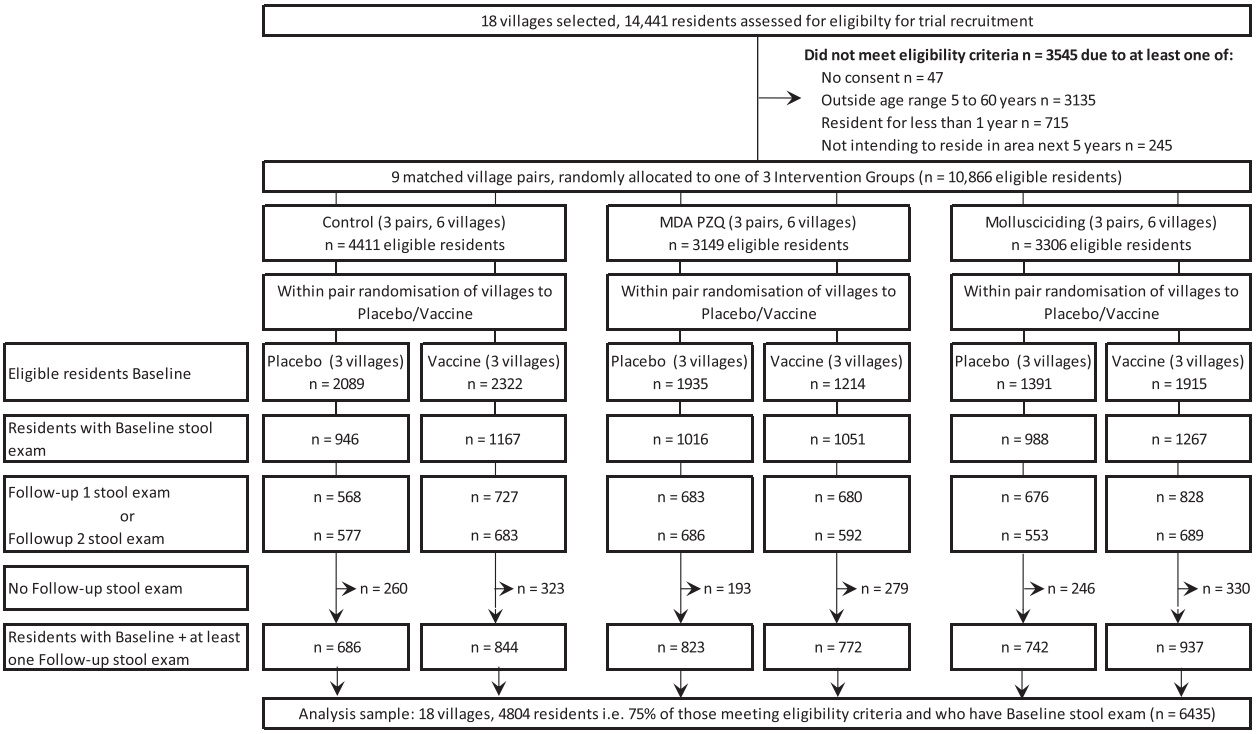

Figure 2. Trial recruitment and follow-up by intervention.
MDA, mass drug administration; PZQ, Praziquantel.

Results

Baseline findings

A total of 18,221 individuals completed an individual medical questionnaire, and 18,163 completed the head-of-household questionnaire. A total of 10,435 eligible individuals aged 5-65 years provided stool specimens for fecal examination. Ultrasonography was conducted on 736 individuals who either reported symptoms of gastrointestinal illness or were believed to have clinical morbidity based on physical examination. Ultrasonography revealed high levels of schistosomiasis-induced morbidity in the schistosomiasis-endemic communities. Left lobe liver enlargement (≥70 mm) was evident in 89.3% of subjects. A total of 25% of the study population had grade II/III liver parenchyma fibrosis, and 13.3% had splenomegaly (≥100 mm). Despite an active schistosomiasis control program in Northern Samar for over 30 years, which included an MDA campaign in the last 5 years, the mean prevalence of schistosomiasis among 10,435 evaluated subjects was 27.1%, and the geometric mean intensity of infection among 2,832 egg-positive subjects was 17.2 EPG of feces.

Trial descriptors

The recruitment and follow-up by intervention are illustrated in Figure 2. A total of 14,441 eligible residents met the selection criterion for entry into the trial among the 18 endemic study villages. A total of 10,866 (75%) individuals were randomly allocated into nine matched pairs comprising three groups of three villages. A total of 75% of the study population had baseline and at least one follow-up stool result. A total of 48% of the study population was male (Table 1). There was no statistically significant difference in the sex ratio among the three trial arms. The majority (74%) were under 40 years of age, with a primary level (73%) of education. Most were farmers (19%), students (24%), or housewives (46%) by occupation. A large number (66%) of study participants reported less than weekly contact with potentially schistosome-contaminated waters (Table 1). At baseline, stool samples were obtained from 497 bovines. The overall prevalence of infection was 42.9%, and intensity was 4.84 EPG. Village prevalence ranged from 6.9% to 64.7%, and intensities from 3.36 to 11.65 EPG. Within the 331 Carabao, the prevalence was 33.5% and intensity 4.20 EPG. Within the 166 cattle, THE prevalence was 61.4%, and the intensity was 5.66 EPG. The bovine vaccine coverage rate was 53% across all follow-ups. Greater overall bovine health, including growth and weight gain, was observed among the vaccinated animals.

Incidence and intensity of human infection

Table 2 depicts human infection (%) by intervention group at baseline and at two subsequent trial follow-up points. For '*Human Controls*,' both bovine-vaccinated villages, and bovine unvaccinated (placebo) villages had significant decreases in human infection at follow-up one (i.e., approximately two years after baseline human treatment), but infection increased slightly at the second follow-up. It is noteworthy that the human infection rate at follow-up two was still lower than the baseline human prevalence. For the '*Human Treatment*,' group the villages that received bovine vaccination had the best outcomes. After baseline human treatment, human infection decreased at both follow-ups. In the villages that received '*Molluscicding*,' again the best outcomes were seen in the villages where the bovines were vaccinated. Human infection declined significantly in subsequent follow-ups ($P = 22.4$; 95% confidence interval [CI] 14.8, 33.9). The results of human infection by village are shown in Figure 3. It is evident that the bovine-vaccinated villages overall had the greatest reductions in human infection following baseline treatment. Vaccination worked additively with either human mass treatment or molluscicding. Table 3 displays human infection intensity (EPG) by intervention group and follow-up (2). The outcomes are consistent with those seen for human reinfection (%).

Table 1
Description of intervention and vaccine groups at baseline, N (%).

	N	Control		Human Treatment		Molluscicide	
		Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine
Sex							
Male	2422	328 (48.0)	428 (50.7)	416 (50.6)	384 (49.7)	379 (51.1)	487 (52.0)
Female	2382	358 (52.0)	416 (49.3)	407 (49.4)	388 (50.3)	363 (48.9)	450 (48.0)
Age							
5-14 years	1903	296 (43.1)	341 (40.4)	320 (38.9)	303 (39.2)	294 (39.6)	349 (37.3)
15-39 years	1538	214 (31.2)	270 (32.0)	274 (33.3)	246 (31.9)	232 (31.3)	302 (32.2)
40-59 years	1363	176 (25.7)	233 (27.6)	229 (27.8)	223 (28.9)	216 (29.1)	286 (30.5)
Education							
Primary or less	3375	502 (73.2)	623 (73.8)	523 (63.6)	534 (69.2)	564 (76.0)	629 (67.1)
Post Primary	1429	184 (26.8)	221 (26.2)	300 (36.4)	238 (30.8)	178 (24.0)	308 (32.9)
Occupation							
Fishing/farming	950	128 (18.7)	153 (18.1)	151 (18.3)	125 (16.2)	179 (24.0)	214 (22.8)
Other occupation	914	79 (11.5)	167 (19.8)	193 (23.5)	242 (31.3)	82 (11.1)	151 (16.1)
Housewife	1937	315 (45.9)	364 (43.1)	315 (38.3)	266 (34.5)	312 (42.1)	365 (39.0)
Student	1003	164 (23.9)	160 (19.0)	164 (19.9)	139 (18.0)	169 (22.8)	207 (22.1)
Water contact[a]							
None	1099	129 (19.0)	316 (37.5)	217 (26.9)	237 (31.7)	87 (12.3)	113 (12.3)
Less than weekly	2615	448 (65.9)	470 (55.8)	434 (53.8)	336 (44.9)	393 (54.2)	534 (58.2)
At least weekly	1005	103 (15.1)	57 (6.8)	156 (19.3)	175 (23.4)	244 (33.7)	270 (29.4)

[a] 85 missing values

Table 2
Human Infection (%) by intervention group, vaccine, and year.

	Baseline		Follow-up 1		Follow-up 2	
Group	No. Tested	Prevalence (95% CI)	No. Tested	Prevalence (95% CI)	No. Tested	Prevalence (95% CI)
Control	**1530**	**24.7 (13.1, 46.8)**	**1295**	**16.7 (7.8, 35.9)**	**1260**	**20.4 (12.3, 33.9)**
Placebo	686	26.2 (11.9, 42.6)	568	21.8 (10.0, 45.8)	577	23.1 (15.2, 35.2)
Vaccine	844	23.4 (13.9, 39.2)	727	16.2 (4.3, 28.2)	683	18.0 (11.8, 27.4)
Human Treatment	**1595**	**22.2 (11.7, 42.0)**	**1363**	**21.5 (16.3, 27.6)**	**1278**	**21.0 (12.6, 34.8)**
Placebo	823	21.0 (12.5, 35.3)	683	23.9 (18.7, 29.1)	686	22.4 (14.8, 33.9)
Vaccine	772	23.4 (13.9, 39.2)	680	20.0 (10.6, 29.4)	592	19.7 (12.9, 30.0)
Molluscicide	**1679**	**35.6 (18.9, 67.2)**	**1504**	**29.5 (13.9, 62.8)**	**1242**	**27.3 (16.5, 45.2)**
Placebo	742	35.7 (21.3, 59.7)	676	37.0 (12.0, 61.9)	553	33.3 (22.0, 50.5)
Vaccine	937	35.5 (21.3, 59.3)	828	25.8 (19.1, 32.5)	689	22.4 (14.8, 33.9)
All Intervention Groups	**4804**	**29.1 (23.1, 35.2)**	**4162**	**24.1 (17.8, 30.5)**	**3780**	**23.4 (19.0, 27.9)**
Placebo	2251	27.0 (20.0, 36.4)	1927	25.6 (17.9, 35.5)	1816	25.9 (20.3, 32.9)
Vaccine	2553	26.9 (20.0, 36.2)	2235	18.8 (13.1, 26.9)	1964	19.9 (15.6, 25.4)

Table 3
Human Infection intensity (geometric eggs per gram) by intervention group and year.

	Baseline		Follow-up 1		Follow-up 2	
Group	No. Positive	EPG (95% CI)	No. Positive	EPG (95% CI)	No. Positive	EPG (95% CI)
Control	**393**	**17.9 (12.4, 25.9)**	**242**	**14.3 (10.3, 19.9)**	**260**	**100 (77, 129)**
Placebo	187	22.3 (13.8, 36.0)	124	15.0 (9.4, 23.9)	133	98 (70, 138)
Vaccine	206	14.7 (11.3, 19.1)	118	13.7 (8.7, 21.4)	127	101 (68, 152)
Human Treatment	**385**	**16.1 (13.1 19.8)**	**299**	**13.2 (10.1, 17.2)**	**271**	**81 (63, 104)**
Placebo	188	14.0 (11.7, 16.6)	163	13.6 (10.4, 17.9)	154	80 (51, 123)
Vaccine	197	18.4 (14.8, 23.0)	136	13.7 (7.8, 20.8)	117	83 (72, 95)
Molluscicide	**621**	**22.7 (18.3, 28.1)**	**464**	**21.2 (13.4, 33.6)**	**354**	**87 (71, 106)**
Placebo	279	23.3 (14.8, 36.7)	250	30.4 (21.0, 43.9)	185	98 (76, 125)
Vaccine	342	22.2 (20.5, 24.0)	214	14.0 (13.0, 15.0)	169	76 (70, 84)
Total	**1399**	**19.3 (16.2, 23.0)**	**1005**	**16.8 (12.6, 22.4)**	**885**	**89 (77, 102)**

CI, confidence interval; EPG, eggs per gram.

Intention-to-treat analysis

Table 4 depicts the intention-to-treat analysis. Overall, bovine vaccination resulted in statistically significant decreases in human infection (relative risk [RR] = 0.75; 95% CI = 0.69 to 0.82) across all trial follow-ups. Snail molluscicide on its own resulted in a statistically significant increase (RR = 1.52; 95% CI = 1.06 to 2.19) in human infection at follow-up one. Human treatment on its own had no statistically significant (RR = 1.13; 95% CI = 0.72 to 1.75) impact on human infection at all follow-ups. However, when bovine vaccination was combined with human mass treatment, there was a significant decrease (RR = 0.84; 95% CI = 0.73 to 0.97) in the human infection across all follow-ups. Combining bovine vaccination was combined with snail molluscicide resulted in the greatest reduction (RR = 0.69; 95% CI = 0.61 to 0.78) in human infection.

Discussion

In the Philippines, the current schistosomiasis drug coverage is estimated to be <40%, and drug compliance is less than 50% [28–31]. Over the past 30 years, MDA has been highly sporadic

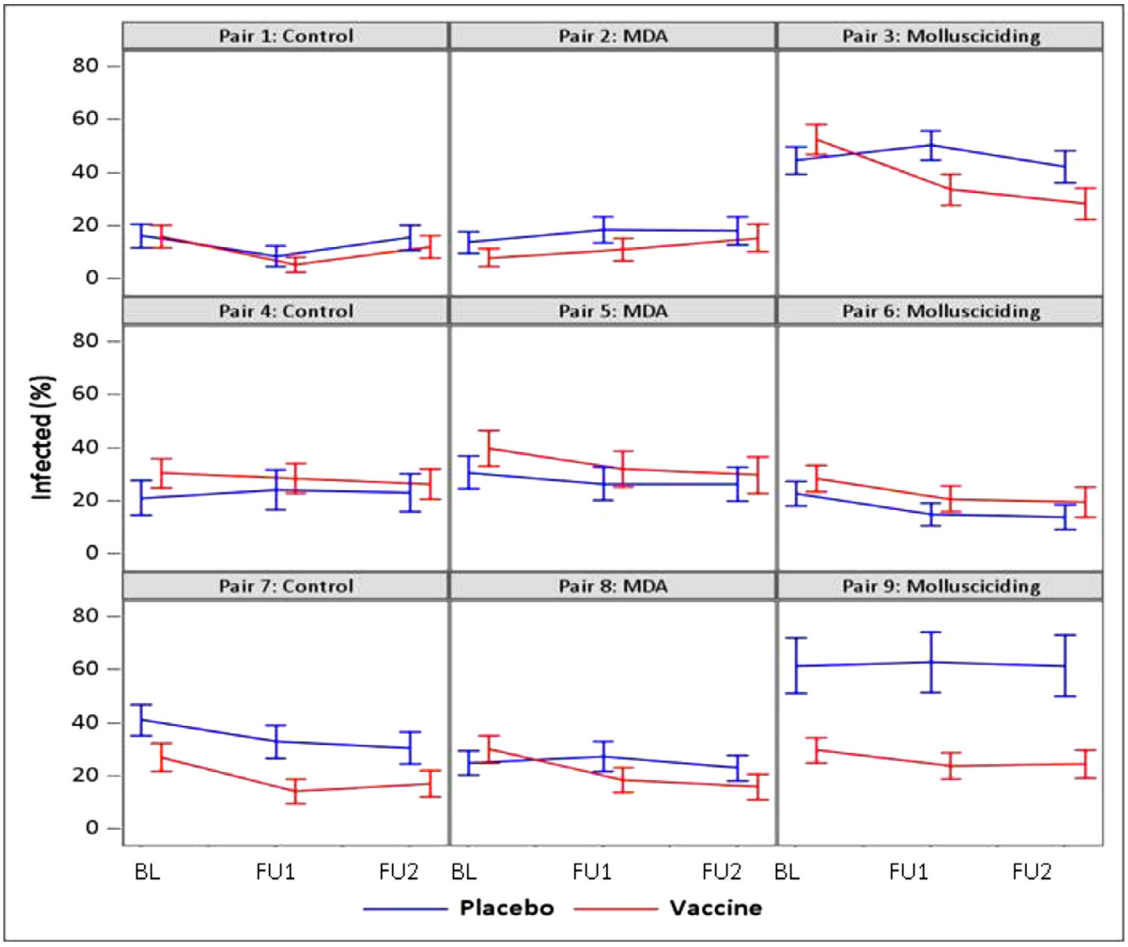

Figure 3. Comparison of percentage of human infected at each time point, for vaccinated vs placebo, within each pair of villages for Control, MDA, and Molluscicide interventions.
Note: BL = Baseline (July-September 2012), FU1 = Follow-up 1 (October-December 2014), FU2 = Follow-up 2 (October-June 2017), Control = No MDA or Molluscicide allocated, MDA = Allocated to mass drug administration in humans.
BL, baseline; FU, follow-up; MDA, mass drug administration.

Table 4
Intention-to-treat analysis of all villages, persons with baseline, and at least one follow-up and incident Infections. Note the effects are adjusted for baseline infection, sex, and age group.

	Follow-up 1		Follow-up 2		All Follow-ups	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Overall effects						
Bovine Vaccine	0.75 (0.67, 0.83)	< 0.001	0.76 (0.68, 0.85)	< 0.001	0.75 (0.69, 0.82)	< 0.001
Human treatment	1.21 (0.84, 1.74)	0.31	1.05 (0.73, 1.51)	0.80	1.13 (0.72, 1.75)	0.54
Molluscicide	1.52 (1.06, 2.19)	0.023	1.25 (0.87, 1.80)	0.23	1.38 (0.89, 2.15)	0.12
Vaccine effect within:						
Control Group	0.73 (0.62, 0.87)	< 0.001	0.75 (0.63, 0.89)	< 0.001	0.74 (0.63, 0.87)	< 0.001
Human treatment	0.83 (0.71, 0.97)	0.022	0.85 (0.72, 1.00)	0.047	0.84 (0.73, 0.97)	0.017
Molluscicide	0.68 (0.60, 0.79)	< 0.001	0.70 (0.60, 0.81)	< 0.001	0.69 (0.61, 0.78)	< 0.001
Human treatment within						
Placebo vaccine	1.14 (0.78, 1.66)	0.51	0.99 (0.67, 1.44)	0.94	1.06 (0.73, 1.53)	0.76
Active vaccine	1.28 (0.88, 1.89)	0.20	1.12 (0.76, 1.64)	0.58	1.20 (0.83, 1.74)	0.34
Molluscicide within						
Placebo Vaccine	1.58 (1.08, 2.30)	0.018	1.30 (0.89, 1.89)	0.18	1.43 (0.99, 2.06)	0.055
Active Vaccine	1.47 (1.01, 2.14)	0.045	1.21 (0.83, 1.77)	0.33	1.33 (0.92, 1.93)	0.12

CI, confidence interval; RR, relative risk.

and highly dependent on donor support [7,8,28–31]. The zoonotic nature of schistosomiasis in the Philippines and in China further complicates control efforts. Bovines have been shown to be responsible for over 80% of the transmission to people, and over 80% of the bovines in the Philippines are heavily infected with the parasite [11–14]. Unlike China, disease transmission in the Philippines is year-round (5 months in China), and it is unlikely that bovines will be replaced by mechanized tractors in the foreseeable future due to poverty [1,9,10]. Therefore, we and others have proposed that a bovine vaccine may be a critical component for a future national control strategy leading to disease elimination [1,9–14].

This is the first trial to provide evidence that bovine vaccination is effective in preventing human schistosomiasis, and we suggest it warrants consideration as part of a future national integrated control strategy to eliminate the disease in the Philippines. The situation in China is less clear. We conducted a similar study in China, but the results were inconclusive, mainly due to the removal or treatment of trial bovines by the government [23]. Most of the animals have now been replaced by mechanized tractors in most endemic zones in a further attempt to eliminate the disease from the country [23]. Thus, it is hoped this strategy will be the final element required to eliminate the disease [1,23]. Given the economic successes in China over the past decade, this was a viable alternative for the national integrated control strategy, but in the Philippines, this is simply not possible given the current economic constraints [23].

To eliminate the disease in the Philippines, the government must first recognize that schistosomiasis is a serious public health problem among the poorest segment of their society [7,8]. With political will, there must come significant financial investment for an integrated control strategy that will comprise annual DOT MDA of endemic communities (with >10% human prevalence) with 60 mg/kg of PZQ (split DOT dose), annual molluscicide (niclosamide 2 g/m^2) of the snail intermediate host in identified 'hotspots' of transmission, annual treatment (30 mg/kg of PZQ) and vaccination (SjCTPI DNA vaccine and protein boost in VacSIM) of bovines with at least 50% coverage [1,10,16,18–21,24–26,32–36]. The total cost of the prime/boost regime is $1.69/buffalo using 'pilot trial' costs. However, we expect these costs to be reduced by 5-10-fold with large-scale production. The benefit of adding bovine vaccination to the current control strategies is the overall reduction in the incidence of schistosomiasis in both humans and bovines. Moreover, greater overall bovine health, including growth and weight gain, was observed among the vaccinated animals.

There were several limitations to this trial. As mentioned, the overall bovine vaccination rate was 53% across all follow-ups. Carabaos are highly prized domestic animals and vital for rice farming in the rural Philippines. Thus, many farmers were reluctant to vaccinate their animals with an experimental vaccine. We anticipate that if the vaccine is formally approved by the government that vaccination rates will improve. Another issue was related to the KK Thick Smear Stool Examination. When the trial was undertaken, the KK technique was (and still is) the World Health Organization's (WHO) gold standard for the detection of human infection of schistosomiasis, although there are issues related to its sensitivity. In a recent meta-analysis by Vaillant et al [36] the authors indicated that conventional diagnostic tools for humans deploying the KK and cathodic circulating antigen methods for *S. mansoni* and urine microscopy for *S. haematobium* have reasonable sensitivity and excellent specificity. Moreover, conventional diagnostic tools are well-accepted, low-cost, and feasible, given their widespread implementation [36]. Newer diagnostic tools, such as molecular-based and immunologic diagnostics, lack sufficient data on sensitivity and specificity, and their utility is further limited by challenges with feasibility and resource implications [36]. The results of this review were used in the recently published (2022) WHO guidelines on the control and elimination of schistosomiasis [37]. In sum, we anticipate that the use of these procedures for all treatment arms would not impact the overall conclusions.

We believe bovine vaccination is the missing component of an integrated control package required for the elimination of schistosomiasis from Asia. Annual bovine vaccination will be required, given their intense exposure and infectivity. The final step for the Philippines will be to improve the bovine vaccination rate and to replicate this trial in several endemic locations. If successful, it may contribute to a new national schistosomiasis control strategy.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

We thank the Australian National Health and Medical Research Council (Award APP1027265), the US National Institutes for Health (Award A1068109), and the Philippine Council for Health Research and Development (FP 170007) for providing funding for this trial.

Ethical approval

Ethical consent for the trial was obtained from the human and animal ethical review boards of the National Department of Health in the Philippines (Institutional Review Board # 2012-13-0) and Griffith University (PBH/24/11/HREC0), Australia. The Research Institute for Tropical Medicine monitored the trial. Written informed consent was obtained from each individual or, for those aged <15 years, from their parents/legal guardians before the commencement of the study. All questionnaires were translated into the local dialect, and responses were back-translated into English. Individuals found to be positive for schistosomiasis, apart from pregnant women, were treated (with DOT) with 60 mg/kg of PZQ (split dose), following the Department of Health National Guideline.[16] Annual human mass treatment with 40 mg/kg of PZQ (single dose) followed both World Health Organization and Department of Health National Guidelines. The trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN12619001048178).

Acknowledgments

We also like to thank the numerous local staff and study participants living in the municipalities of Laoang and Palapag for their enormous contributions to conducting the field trial. In memory of Dr Remigio Olveda, MD, and Mr Julius Chy, who contributed greatly to the coordination of the field studies. Gone but not forgotten old friends!

Author contributions

Concept and design: AR, DH, DG, GW, and DM. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: AR, DH, GW, and DM. Critical revision of the manuscript for important intellectual content: AR, GW, DM, and DG. Obtained funding: AR, RO, YL, DH, and DG. Administration, technical or material support: AR, DH, GW, RO, AI, DC, JC, JG, and LS. Supervision: AR, RO, DH, YL, DC, and JC. The authors declare no conflict of interest, and all authors read and approved the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.01.037.

References

[1] Ross AG, Olveda RM, Li Y. An audacious goal: the elimination of schistosomiasis in our lifetime through mass drug administration. *Lancet* 2015;**385**:2220–1. doi:10.1016/S0140-6736(14)61417-3.

[2] Olveda DU, McManus DP, Ross AG. Mass drug administration and the global control of schistosomiasis: successes, limitations and clinical outcomes. *Curr Opin Infect Dis* 2016;**29**:595–608. doi:10.1097/QCO.0000000000000312.

[3] Delos Trinos JPCR, Wulandari LPL, Clarke N, Belizario V Jr, Kaldor J, Nery SV. Prevalence of soil-transmitted helminth infections, schistosomiasis, and lymphatic filariasis before and after preventive chemotherapy initiation in the Philippines: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2021;**15**:e0010026. doi:10.1371/journal.pntd.0010026.

[4] Levecke B, Vlaminck J, Andriamaro L, Ame S, Belizario V, Degarege A, Engels D, Erko B, Garba AD, Kaatano GM, Mekonnen Z, Montresor A, Olliaro P, Pieri OS, Sacko M, Sam-Wobo SO, Tchuem Tchuenté LA, Webster JP, Vercruysse J. Evaluation of the therapeutic efficacy of praziquantel against schistosomes in seven countries with ongoing large-scale deworming programs. *Int J Parasitol Drugs Drug Resist* 2020;**14**:183–7. doi:10.1016/j.ijpddr.2020.10.003.

[5] Ogongo P, Nyakundi RK, Chege GK, Ochola L. The road to elimination: current state of schistosomiasis research and progress towards the end game. *Front Immunol* 2023;**13**:846108. doi:10.3389/fimmu.2022.846108.

[6] King CH, Kittur N, Binder S, Campbell CH, N'Goran EK, Meite A, Utzinger J, Olsen A, Magnussen P, Kinung'hi S, Fenwick A, Phillips AE, Gazzinelli-Guimaraes PH, Dhanani N, Ferro J, Karanja DMS, Mwinzi PNM, Montgomery SP, Wiegand RE, Secor WE, Hamidou AA, Garba A, Colley DG. Impact of different mass drug administration strategies for gaining and sustaining control of schistosoma mansoni and schistosoma haematobium infection in Africa. *Am J Trop Med Hyg* 2020;**103**:14–23. doi:10.4269/ajtmh.19-0829.

[7] Olveda DU, Li Y, Olveda RM, Lam AK, McManus DP, Chau TN, Harn DA, Williams GM, Gray DJ, Ross AG. Bilharzia in the Philippines: past, present, and future. *Int J Infect Dis* 2014;**18**:52–6. doi:10.1016/j.ijid.2013.09.011.

[8] Olveda RM, Tallo V, Olveda DU, Inobaya MT, Chau TN, Ross AG. National survey data for zoonotic schistosomiasis in the Philippines grossly underestimates the true burden of disease within endemic zones: implications for future control. *Int J Infect Dis* 2016;**45**:13–17. doi:10.1016/j.ijid.2016.01.011.

[9] Ross AG, Olveda RM, Acosta L, Harn DA, Chy D, Li Y, Gray DJ, Gordon CA, McManus DP, Williams GM. Road to the elimination of schistosomiasis from Asia: the journey is far from over. *Microbes Infect* 2013;**15**:858–65. doi:10.1016/j.micinf.2013.07.010.

[10] Ross AG, Chau TN, Inobaya MT, Olveda RM, Li YS, Harn DA. A new global strategy for the elimination of schistosomiasis. *Int J Infect Dis* 2017;**54**:130–7. doi:10.1016/j.ijid.2016.09.023.

[11] Gordon CA, Acosta LP, Gray DJ, Olveda RM, Jarilla B, Gobert GN, Ross AG, McManus DP. High prevalence of *Schistosoma japonicum* infection in Carabao from Samar Province, the Philippines: implications for transmission and control. *PLoS Negl Trop Dis* 2012;**6**:e1778. doi:10.1371/journal.pntd.0001778.

[12] Gordon CA, Acosta LP, Gobert GN, Jiz M, Olveda RM, Ross AG, Gray DJ, Williams GM, Harn D, Li Y, McManus DP. High prevalence of *Schistosoma japonicum* and *Fasciola gigantica* in bovines from Northern Samar, the Philippines. *PLoS Negl Trop Dis* 2015;**9**:e0003108. doi:10.1371/journal.pntd.0003108.

[13] Jiz M, Mingala C, Fu ZQ, Adriatico M, Lu K, Jarilla B, Sagliba M, Moreno A, Park S, Lin JJ, Olveda R, Kurtis JD, Wu HW. High prevalence of Schistosoma japonicum by perfusion in naturally exposed water buffalo in a region of the Philippines endemic for human schistosomiasis. *PLoS Negl Trop Dis* 2021;**15**:e0009796. doi:10.1371/journal.pntd.0009796.

[14] Jumawan JC, Estaño LA. Prevalence of *Schistosoma japonicum* in bovines and Oncomelania hupensis quadrasi from ricefields surrounding Lake Mainit. *Philippines. J Parasit Dis* 2021;**45**:851–8. doi:10.1007/s12639-021-01372-3.

[15] Dalisay SNM, Belizario VY, Joe JAS, Lumangaya CR, Cruz RD. Critical medical ecology and intersectionality perspectives in schistosomiasis prevention and control in selected communities in Mindanao, the Philippines. *J Biosoc Sci* 2022. doi:10.1017/S0021932021000766.

[16] Rollinson D, Sankar G, Stephens M, Gouvras A, Waltz J, Tchuem Tchuenté LA, Imtiaz R. Increasing efficiencies from integrating control and elimination programmes for soil-transmitted helminths and schistosomiasis. *Int Health* 2022;**14**:111–12. doi:10.1093/inthealth/ihab029.

[17] Lemos M, Fançony C, Moura S, Mirante C, Sousa P, Barros H, Nery S, Brito M. Integrated community-based intervention for urinary schistosomiasis and soil-transmitted helminthiasis in children from Caxito. *Angola. Int Health* 2020;**12**:86–94. doi:10.1093/inthealth/ihz055.

[18] Raso G, Essé C, Dongo K, Ouattara M, Zouzou F, Hürlimann E, Koffi VA, Coulibaly G, Mahan V, Yapi RB, Koné S, Coulibaly JT, Meïté A, Guéhi-Kabran MC, Bonfoh B, N'Goran EK, Utzinger J. An integrated approach to control soil-transmitted helminthiasis, schistosomiasis, intestinal protozoa infection, and diarrhea: protocol for a cluster randomized trial. *JMIR Res Protoc* 2018;**7**:e145. doi:10.2196/resprot.9166.

[19] Williams GM, Sleigh AC, Li Y, Feng Z, Davis GM, Chen H, Ross AG, Bergquist R, McManus DP. Mathematical modelling of schistosomiasis japonica: comparison of control strategies in the People's Republic of China. *Acta Trop* 2002;**82**:253–62. doi:10.1016/s0001-706x(02)00017-7.

[20] Gray DJ, McManus DP, Li Y, Williams GM, Bergquist R, Ross AG. Schistosomiasis elimination: lessons from the past guide the future. *Lancet Infect Dis* 2010;**10**:733–6. doi:10.1016/S1473-3099(10)70099-2.

[21] Gray DJ, Li YS, Williams GM, Zhao ZY, Harn DA, Li SM, Ren MY, Feng Z, Guo FY, Guo JG, Zhou J, Dong YL, Li Y, Ross AG, McManus DP. A multi-component integrated approach for the elimination of schistosomiasis in the People's Republic of China: design and baseline results of a 4-year cluster-randomised intervention trial. *Int J Parasitol* 2014;**44**:659–68. doi:10.1016/j.ijpara.2014.05.005.

[22] McManus DP, Bieri FA, Li YS, Williams GM, Yuan LP, Henglin Y, Du ZW, Clements AC, Steinmann P, Raso G, Yap P, Magalhães RJ, Stewart D, Ross AG, Halton K, Zhou XN, Olveda RM, Tallo V, Gray DJ. Health education and the control of intestinal worm infections in China: a new vision. *Parasit Vectors* 2014;**7**:344. doi:10.1186/1756-3305-7-344.

[23] Williams GM, Li YS, Gray DJ, Zhao ZY, Harn DA, Shollenberger LM, Li SM, Yu X, Feng Z, Guo JG, Zhou J, Dong YL, Li Y, Guo B, Driguez P, Harvie M, You H, Ross AG, McManus DP. Field testing integrated interventions for schistosomiasis elimination in the People's Republic of China: outcomes of a multi-factorial cluster-randomized controlled trial. *Front Immunol* 2019;**10**:645. doi:10.3389/fimmu.2019.00645.

[24] Da'Dara AA, Li C, Yu X, Zheng M, Zhou J, Shollenberger LM, Li YS, Harn DA. Prime-Boost Vaccine Regimen for SjTPI and SjC23 Schistosome Vaccines, Increases Efficacy in Water Buffalo in a Field Trial in China. *Front Immunol* 2019;**10**:284. doi:10.3389/fimmu.2019.00284.

[25] Grenfell RF, Shollenberger LM, Samli EF, Harn DA. Vaccine self-assembling immune matrix is a new delivery platform that enhances immune response to recombinant HBsAg in mice. *Clin Vaccine Immunol* 2015;**22**:336–43. doi:10.1128/CVI.00714-14.

[26] Ross AG, Olveda RM, Chy D, Olveda DU, Li Y, Harn DA, Gray DJ, McManus DP, Tallo V, Chau TN, Williams GM. Can mass drug administration lead to the sustainable control of schistosomiasis? *J Infect Dis* 2015;**211**:283–9. doi:10.1093/infdis/jiu416.

[27] Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013;**22**:661–70. doi:10.1177/0962280211427759.

[28] Inobaya MT, Olveda RM, Tallo V, McManus DP, Williams GM, Harn DA, Li Y, Chau TN, Olveda DU, Ross AG. Schistosomiasis mass drug administration in the Philippines: lessons learnt and the global implications. *Microbes Infect* 2015;**17**:6–15. doi:10.1016/j.micinf.2014.10.006.

[29] Olveda DU, Inobaya M, McManus DP, Olveda RM, Vinluan ML, Ng SK, Harn DA, Li Y, Guevarra JR, Lam AK, Ross AG. Biennial versus annual treatment for schistosomiasis and its impact on liver morbidity. *Int J Infect Dis* 2017;**54**:145–9. doi:10.1016/j.ijid.2016.10.001.

[30] Inobaya MT, Chau TN, Ng SK, MacDougall C, Olveda RM, Tallo V, Landicho JM, Malacad CM, Aligato MF, Guevarra JR, Ross AG. Mass drug administration and the sustainable control of schistosomiasis: community health workers are vital for global elimination efforts. *Int J Infect Dis* 2018;**66**:14–21. doi:10.1016/j.ijid.2017.10.023.

[31] Inobaya MT, Chau TN, Ng SK, MacDougall C, Olveda RM, Tallo V, Landicho JM, Malacad CM, Aligato MF, Guevarra JR, Ross AG. Mass drug administration and the sustainable control of schistosomiasis: a comprehensive evaluation of patient compliance in the Philippines. *Clinical Microbiology and Infection. Parasit Vectors* 2018;**11**:441. doi:10.1186/s13071018-3022-2.

[32] Andrade-Pacheco R, Rerolle F, Lemoine J, Hernandez L, Meïté A, Juziwelo L, Bibaut AF, van der Laan MJ, Arnold BF, Sturrock HJW. Finding hotspots: development of an adaptive spatial sampling approach. *Sci Rep* 2020;**10**:10939. doi:10.1038/s41598-020-67666-3.

[33] Gomez DC, Anacta N. A New Method to Test Molluscicides against the Philippine Schistosomiasis Snail Vectors. *J Parasitol Res* 2020;**2020**:3827125. doi:10.1155/2020/3827125.

[34] Onasanya A, Bengtson M, Oladepo O, Van Engelen J, Diehl JC. Rethinking the top-down approach to schistosomiasis control and elimination in Sub-Saharan Africa. *Front Public Health* 2021;**9**:622809. doi:10.3389/fpubh.2021.622809.

[35] Assaré RK, N'Tamon RN, Bellai LG, Koffi JA, Mathieu TI, Ouattara M, Hürlimann E, Coulibaly JT, Diabaté S, N'Goran EK, Utzinger J. Characteristics of persistent hotspots of Schistosoma mansoni in western Côte d'Ivoire. *Parasit Vectors* 2020;**13**:337. doi:10.1186/s13071-020-04188-x.

[36] Vaillant MT, Philippy F, Barré J, Bulaev D, Garba AT. Diagnostic tests for schistosomiasis for low prevalence settings: a systematic review and meta-analysis. *medRxiv* 2021;**9**:2021 –05. doi:10.1101/2021.05.05.21256678.

[37] Lo NC, Bezerra FSM, Colley DG, Fleming FM, Homeida M, Kabatereine N, Kabole FM, King CH, Mafe MA, Midzi N, Mutapi F, Mwanga JR, Ramzy RMR, Satrija F, Stothard JR, Traoré MS, Webster JP, Utzinger J, Zhou XN, Danso-Appiah A, Eusebi P, Loker ES, Obonyo CO, Quansah R, Liang S, Vaillant M, Murad MH, Hagan P, Garba A. Review of 2022 WHO guidelines on the control and elimination of schistosomiasis. *Lancet Infect Dis* 2022;**22**:e327–35. doi:10.1016/S1473-3099(22)00221-3.