Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial

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Summary

Background Despite WHO recommendations to offer pregnant women treatment with praziquantel, many nations continue to withhold treatment, awaiting data from controlled trials addressing safety and efficacy. The objectives of this study were to assess whether treatment of pregnant women with schistosomiasis at 12–16 weeks gestation leads to improved maternal and newborn outcomes and to collect maternal and newborn safety data.

Methods This phase 2, randomised, double-blind, placebo-controlled trial was done in 72 baranguays (villages) serviced by six municipal health centres in a schistosomiasis endemic region of northeastern Leyte, Philippines. Pregnant women (at 12–16 weeks gestation) who were otherwise healthy but infected with *Schistosoma japonicum* were enrolled and randomly assigned (1:1) to receive either over-encapsulated praziquantel (total dose 60 mg/kg given as two split doses) or placebo. Participants, investigators, midwives, and laboratory staff were all masked to treatment. The primary outcome was birthweight. Safety data were collected including immediate reactogenicity, post-dosing toxicology ascertained 24 h after study drug administration, and maternal and newborn serious adverse events. Analysis followed the intention-to-treat principle. Analyses were done using hierarchical generalised linear models to adjust for identified confounders and account for potential clustering of observations within villages and municipalities. This trial is registered with ClinicalTrials.gov, number NCT00486863.

Findings Between Aug 13, 2007, and Dec 3, 2012, 370 pregnant women were enrolled and randomly assigned to each treatment group (184 to the placebo group, 186 to the praziquantel group). Most women had low-intensity infections (n=334, 90%). Treatment with praziquantel did not have a significant effect on birthweight (2·85 kg in both groups, β=–0·002 [95% CI –0·088 to 0·083]; p=0·962). Treatment was well tolerated with reactogenicity rates similar to those seen in non-pregnant participants (severe reactions occurred in five patients in the praziquantel group and two in the placebo group, and included headache, fever, and malaise). There were no significant differences in key safety outcomes including abortion, fetal death in utero, and congenital anomalies.

Interpretation Results from this study provide important data from a controlled trial in support of the expansion of treatment policies to include pregnant women as recommended by WHO.

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Introduction

Over 200 million individuals are infected with one of three species of schistosomes globally,[1] including an estimated 40 million women of reproductive age. Schistosomiasis is a significant cause of morbidity and mortality in low-income and middle-income countries, despite the availability of effective pharmacological therapy with praziquantel.[2] Praziquantel was released in 1979, but was never studied in pregnant or lactating women and remains a US Federal Drug Administration pregnancy class B drug. Its class B designation is based on numerous animal studies supporting its safety,[3,4] but there is a lack of well controlled trials during human pregnancy.

In 2002, a WHO report recommended that all schistosomiasis-infected pregnant and lactating women be considered high-risk groups and be offered treatment with praziquantel individually or during treatment campaigns.[5–7] This recommendation was reissued in 2006 as part of the *WHO guidelines for preventative chemotherapy for helminthiasis*,[2] in which it was recommended that pregnant and lactating women be included in mass drug administration campaigns. These recommendations were largely motivated by the expected progression of both end-organ morbidity and anaemia if women remained untreated during repeated cycles of pregnancy and lactation, the demonstrated safety in animal models of pregnancy, and the expected safety in human beings based on inadvertent exposures during human pregnancy. Although some nations, particularly in Africa, have adopted this policy, many others, including the Philippines, have not, awaiting safety data from well controlled trials in human beings. Therefore, millions of women of reproductive age are not treated for many years during repeated cycles of pregnancy and lactation.

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Research in context

Evidence before this study

We searched PubMed from inception until Aug 9, 2015, for clinical trials testing the use of praziquantel in pregnancy, using the search terms "praziquantel" and "pregnancy" and "schistosomiasis" and also for observational studies using the search terms "pregnancy" and "schistosomiasis" restricted to publications in English. In 2002, based on post-marketing surveillance data, the expected morbidity due to untreated schistosomiasis, and a concern that randomised controlled trials would not be done, an informal consultation convened by WHO recommended treating pregnant women with praziquantel. After the WHO recommendation, a four-group randomised controlled trial done in Uganda treated pregnant women (mean gestational age 26·6 weeks) with praziquantel, albendazole, praziquantel plus albendazole, or placebo. All women were randomly assigned and treated, irrespective of infection status. That study did not show a significant effect on maternal anaemia or birthweight, but did provide evidence about the safety of praziquantel given in the late second trimester or early third trimester at a dose of 40 mg/kg. Additionally, a study done in Tanzania found an increased risk of anaemia in pregnant women with high-intensity *Schistosoma mansoni* infection. Despite this, many nations, including the Philippines and those in sub-Saharan Africa, have not adopted the WHO recommendation, awaiting further safety data from controlled trials.

Added value of this study

Results from this trial provide the first evidence from a randomised controlled trial that targeting women known to be infected with schistosomiasis is safe. This result is significant because treatment causes a profound inflammatory response among infected individuals. Additionally, women were treated much earlier in pregnancy at 12–16 weeks gestation compared with the only other randomised controlled trial of praziquantel treatment during pregnancy. Further, in this randomised controlled trial, praziquantel was provided at a higher dose of 60 mg/kg as recommended for *Schistosoma japonicum* infection. This dose, even given much earlier in pregnancy, was found to be safe. With respect to efficacy, results from this study suggest that treatment might improve both maternal and newborn iron status, likely through amelioration of anaemia of inflammation allowing better absorption and distribution of prenatal iron supplements. This study is the first to show potential benefit of treating schistosomiasis during pregnancy.

Implications of all the available evidence

These results, together with the recently completed randomised controlled trial done in Uganda, provide key evidence about the safety of praziquantel during human pregnancy. Though treatment did not affect birthweight in this study nor the Ugandan trial, we found that treatment did affect maternal and newborn iron status. Results from these studies should allow WHO to strengthen its recommendation to treat women during pregnancy based on available new safety data from two randomised controlled trials as well as possible efficacy with respect to iron status. Partnering with departments of health in schistosomiasis endemic communities will be crucial to change the use of praziquantel in mass drug administration campaigns, during which many women of reproductive age are currently excluded.

In addition to the lack of safety data in human beings, the specific effect of human schistosomiasis on pregnancy outcomes remains understudied. Schistosomiasis has been implicated as a contributor to undernutrition[8–14] in non-pregnant patients. Schistosomiasis culminates in undernutrition through effects on appetite[15] (anorexia and symptomatology) and inflammation-mediated cachexia.[16] Schistosomiasis also contributes to the global burden of anaemia, largely through anaemia of inflammation.[10,12,17,18] Additionally, studies support the role of schistosomiasis in iron deficiency anaemia at higher intensities of infection because individuals experience occult blood loss in urine and stool.[19–22]

In view of the demonstrated morbidity among non-pregnant patients, a few studies have sought to address the effect of schistosomiasis infection in human pregnancy.[23,24] One randomised controlled trial done in Uganda examined the effect of praziquantel given to pregnant women during the second or third trimester (mean gestational age 26·6 weeks).[24] That study differed from the trial reported here because women who were and were not infected with schistosomiasis were included in the randomised sample. The trial did not show a significant effect of praziquantel on maternal anaemia or birthweight, even among the roughly 18% of women who were infected with *Schistosoma mansoni*. No studies have examined whether treatment earlier in gestation improves pregnancy outcomes, none have examined the effect of treatment for *Schistosoma japonicum*, and none have examined use of the higher dose of praziquantel recommended for *S japonicum*.

The objectives of this study were to assess whether treatment of pregnant women with schistosomiasis at 12–16 weeks gestation leads to improved maternal and newborn outcomes including birthweight (primary endpoint) and both maternal and newborn anaemia and iron status, and to collect safety data addressing immediate reactogenicity, adverse events during pregnancy, and adverse newborn outcomes such as congenital anomalies. We hypothesised that treatment of *S japonicum* during pregnancy would lead to higher newborn birthweight by improving maternal appetite and nutritional status, higher maternal haemoglobin and bioavailable iron through decreasing the risk for anaemia

of inflammation during pregnancy, and improved newborn iron stores through greater iron bioavailability to the developing fetus.

Methods

Study design and participants

This study was a phase 2, double-blind, placebo-controlled trial addressing the effects of praziquantel given at 12–16 weeks gestation on maternal and newborn birth outcomes (efficacy) and initial safety and toxicology.

The study was done in 72 baranguays (villages) serviced by six municipal health centres in a schistosomiasis endemic region of northeastern Leyte, Philippines. At this study site, soil-transmitted helminths, but not malaria, are endemic and the prevalence of HIV is less than 0·1%.[25]

Informed consent for screening procedures was obtained by one of 12 midwives servicing the six municipal health centres who were members of the study staff. Initial eligibility screening included a urine pregnancy test and three stool samples collected on different days for the quantification of *S japonicum* and soil-transmitted helminth eggs using the Kato-Katz method. Kato-Katz analysis was done by trained medical technologists at the study laboratory in Palo. Two Kato-Katz slides were examined for each sample within 30 min for hookworm and up to 24 h later for other helminth infections including schistosomiasis. Each stool sample was quantified in duplicate and the mean determined. Intensity of infection was determined as the mean of the three samples. *S japonicum* infection intensity was categorised as low (0–99 eggs per g of stool), moderate (100–399 eggs per g), or high (400 or more eggs per g). The second phase of screening was done at Remedios Trinidad Romualdez Hospital in Tacloban, Leyte. The study physician took a history and did a physical examination and a transabdominal ultrasound to assess fetal viability and estimate gestational age. Additionally, a blood sample was obtained before administration of the study drug to measure serum chemistries (renal and liver function tests) and a complete blood count. Weight, height, and other anthropometric measures were made including thigh skin-fold thickness as described previously.[26,27]

Women were eligible for the trial if they provided informed consent and were infected with *S japonicum*, aged 18 years or older, otherwise healthy as established by physician history, physical examination and laboratory studies, and pregnant at 12–16 weeks gestation with a live, singleton, intrauterine fetus. Pregnancies with estimated gestation less than 12 weeks were scheduled to return, as were women with an acute medical condition that could potentially be addressed before 12–16 weeks gestation.

All women were offered treatment for schistosomiasis and soil-transmitted helminths at the conclusion of lactation because it was the Philippines Department of Health policy to defer treatment until cessation of breast-feeding. Infants who had a medical disorder or malnutrition diagnosed during the newborn period were referred for care. The study was separately approved by both the Rhode Island Hospital Institutional Review Board in Providence, RI, USA, and the ethics review board of the Research Institute of Tropical Medicine in Manila, Philippines.

Randomisation and masking

Women who met eligibility criteria were randomly assigned (1:1) to receive either over-encapsulated praziquantel (two doses of 30 mg/kg) or over-encapsulated placebo (dextrose), separated by 3 h in a double-blind fashion. The study drug was compounded by the Rhode Island Hospital Pharmacy using praziquantel tablets obtained from Schering-Plough (Kenilworth, NJ, USA). Dextrose and gelatin capsules were provided by Gallipot. Both provided certificates of analysis for these compounds before study initiation. Two capsule doses were made which were differentiated by colour, containing 300 mg or 150 mg to allow for optimal dosing by weight. Statisticians at the EMMES Corporation, the statistical and data coordinating centre for the study, randomly allocated study numbers in blocks of six. Study drug was administered at Remedios Trinidad Romualdez Hospital. Participants, investigators, midwives, and laboratory staff were all masked to treatment.

Procedures

After giving each of the split doses, participants were actively assessed for adverse drug reactions and then observed in the hospital for 24 h. Before discharge, a repeat blood sample was drawn for serum chemistries and a complete blood count. Additionally, after about 100 participants were recruited, the protocol was amended to include two additional blood samples collected at varying times post-dosing for population pharmacokinetics, the results of which will be reported elsewhere. About 10–14 days after discharge, participants were visited at their home by study staff to elicit any symptoms experienced since hospital discharge.

Participants had two scheduled follow-up visits before delivery, both within 2 weeks of 22 weeks and 32 weeks gestation at Remedios Trinidad Romualdez Hospital. Stool was collected at the 22 week visit for assessment of parasitological cure. Additionally, women were seen by the study obstetrician and a detailed history and physical examination were taken, including measures of nutritional status as described above. At the 32 week visit, the history, physical examination, and nutritional measures were repeated, a blood sample was collected for complete blood count and analytes capturing iron (ferritin, serum transferrin receptor [sTfR]) and inflammatory markers (C-reactive protein, hepcidin, tumour necrosis factor α, interferon λ, interleukin 6, and

interleukin 1). Serum samples were aliquoted and stored at –80°C. Bioactive serum hepcidin (DRG Hepcidin 25 bioactive ELISA [EIA-5258]) was measured according to manufacturer's instructions. Other analytes were quantified using a multiplex bead-based platform (Bio-Rad, Hercules, CA, USA), as described previously.[8] A urine sample was collected to screen for pre-eclampsia and urinary tract infections. Women were scheduled for additional visits as needed based on obstetrician-identified diagnoses and were also asked to come to Remedios Trinidad Romualdez Hospital for unscheduled visits for other concerns that arose.

Mothers gave birth in one of the six municipal health centres or were referred to Remedios Trinidad Romualdez Hospital if indicated. Gestational age at birth was assessed by a modified Dubowitz scoring system developed by Ballard and colleagues.[28] For deliveries that occurred at home based on maternal preference or inability to get to a municipal health centre, mothers contacted the study midwife who visited the mother within 48 h of delivery.

Both mother and newborn returned to Remedios Trinidad Romualdez Hospital at 2–6 days of life for follow-up. The study paediatrician took their history and did a physical examination and a heel stick blood sample was obtained for newborn screening, complete blood count, and the aforementioned iron and inflammatory analytes. Study close-out occurred at Remedios Trinidad Romualdez Hospital at 28 days of life, at which point the paediatrician again took a history and did a physical examination and referred the newborn for any identified concerns.

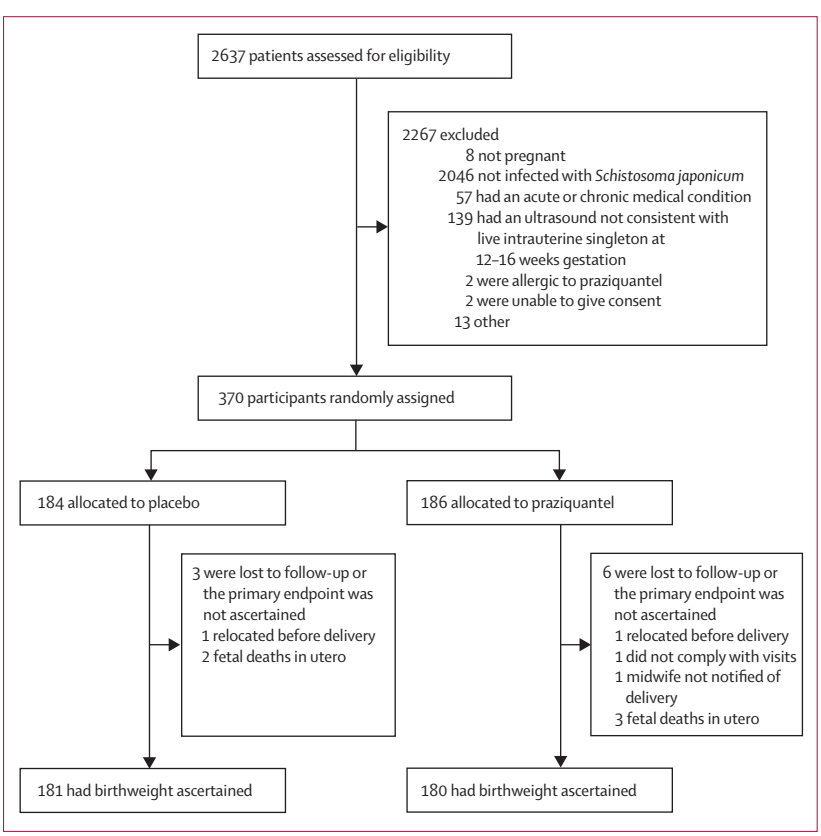

Figure: **Trial profile**

Outcomes

The primary outcome was birthweight. Newborns were weighed within 48 h of delivery on a Tanita model BD-585 portable scale (Arlington Heights, MD, USA) to within 10 g. Birthweights taken 24–48 h after delivery were corrected by a factor of +2%, to obtain the estimated weight at birth. Secondary outcomes included low birthweight (defined as weight <2·5 kg) and small for gestational age (used as an indicator for possible intrauterine growth restriction). Small for gestational age was based on the gestational age determined at the 12–16 week ultrasound and was defined as gestational age adjusted birthweight that was less than the 10th percentile based on the multiracial Williams curves.[29] Other secondary efficacy outcomes included change in maternal nutritional status, maternal anaemia (haemoglobin <11·0 g/dL), haemoglobin, and iron status at 32 weeks gestation, newborn haemoglobin and iron status measured on a heel stick blood sample at 2–6 days of life, prematurity defined as gestation less than 37 weeks, and parasitological cure rate as defined by the percentage of participants with 0 eggs per g at 22 weeks gestation, treatment success as defined by more than 90% reduction in *S japonicum* egg count from screening to 22 weeks gestation, and percent change in *S japonicum* eggs per g from baseline to 22 weeks gestation.

Safety outcomes included toxicity to maternal bone marrow, kidney, and liver as measured by laboratory parameters collected just before, and 24 h after dosing, maternal seizures, immediate toxic effects to the fetus as assessed by abortion (fetal demise before 20 weeks gestation), live birth rate, and newborn congenital anomalies.

Statistical analysis

The initial target sample size was 500 pregnant women, with a plan to enrol equal numbers of women with low-intensity and moderate-intensity or high-intensity infections with *S japonicum*. The protocol was modified to omit this requirement when it was noted that the prevalence of moderate-intensity and high-intensity infections was much lower than expected. The protocol was later modified to decrease the target enrolment to 370 because of a concern about study duration and because the overall prevalence of *S japonicum* infection was lower than originally anticipated. This approach was tenable because attrition rates were significantly lower than originally anticipated such that the primary outcome was still captured on more than the planned number of participants (162 in each group) needed to detect a

difference in birthweight of 125 g, with a type I error of 0·05, and a power of 0·80.

Household socioeconomic status was captured using a questionnaire developed for use in this population, as described previously.[30] A summary score reflected numeric weights assigned to socioeconomic status questionnaire items as described by Filmer and colleagues,[31] using the FACTOR procedure in SAS 9.3 (Cary, NC, USA). Summary socioeconomic status scores were categorised by quartile and compared by treatment group.

The following other prespecified covariates were assessed as potential confounders: maternal age, maternal weight and height at enrolment, smoking status at enrolment (yes or no), reported alcohol intake at enrolment (one to two, three to five, six to eight, nine to ten, and more than ten glasses of alcohol consumed per week), newborn sex, reported compliance with iron supplementation, intensity of infection with *S japonicum* at enrolment (low, medium, high, as described above) and treated as an ordinal variable in analyses, obstetrical history with an adverse event (defined as having one or more occurrences of a miscarriage, abortion, or stillbirth) treated as a dichotomous variable in analyses, and intensity of infection with geohelminths at enrolment defined using WHO criteria.

Outcomes and potential confounders were compared between praziquantel and placebo groups at enrolment using χ^2 and Wilcoxon two-sample or *t* tests. Potential confounders were considered for inclusion in final models if associated with treatment at an α level of 0·10. None met this criteria such that outcomes are presented by treatment group without adjustment for potential confounders.

Primary and secondary efficacy analyses were done using hierarchical generalised linear models to account for potential clustering of observations within villages and municipalities. Models of each outcome included a main effect for treatment and random intercepts for villages and health centres. Intraclass correlations were estimated from the covariance parameters for each random effect to assess the proportion of the total variance attributable to village or health centre. Covariance parameter estimates were assessed for significance with a Wald or likelihood ratio test. Random effects whose intercept variance estimates were not significantly different from zero at the α level of 0·05 were removed from the final model. Standard model diagnostics were used to assess model assumptions of linearity, normality, and constant variance of residuals. Outcomes were log-transformed if necessary to avoid violation of regression assumptions. Analyses were done using the MIXED procedure for continuous outcomes and NLMIXED procedure for binary outcomes in SAS 9.3. Primary efficacy models additionally assessed the interaction of infection intensity with *S japonicum* (eggs per g) at enrolment with treatment allocation, to establish whether baseline intensity of infection modified the relation between treatment and birthweight.

Analyses were done on an intention-to-treat population. The trial was registered with ClinicalTrials.gov, number NCT00486863.

Role of the funding source

The study funder supported the protocol development in collaboration with the investigators and engaged a data management and statistical analyses partner, EMMES Corporation, which was responsible for design of databases, summary reports for the data, safety, and monitoring board meetings, and final statistical analyses for this report. The funder had no role in generation of hypotheses, data collection, data analysis, data interpretation, or writing of the report. The authors, with the exception of NW, did not have access to study data until all databases were locked and the analyses reported in the manuscript were complete. The corresponding author had access to the locked dataset and had final responsibility for the decision to submit for publication.

	Placebo (n=184)	Praziquantel (n=186)
Age, years	25·9 (6·26)	26·2 (6·60)
Socioeconomic quartile		
1st quartile	21 (11%)	26 (14%)
2nd quartile	67 (36%)	73 (39%)
3rd quartile	46 (25%)	46 (25%)
4th quartile	50 (27%)	41 (22%)
Current smoking status		
No	183 (99%)	185 (99%)
Yes	1 (1%)	1 (1%)
Current alcohol consumption		
No	48 (26%)	39 (21%)
Yes	136 (74%)	147 (79%)
Height (cm)	147·1 (5·8)	147·8 (5·2)
Weight (kg)	47·3 (7·5)	47·8 (7·0)
Schistosoma japonicum at screening (eggs per g)*	10·00 (3·33–30·00)	10·00 (3·33–30·00)
S japonicum at screening (eggs per g)	40·4 (95·3)	32·7 (58·3)
Ascaris lumbricoides at screening (eggs per g)*	475·0 (0·00–7923·33)	803·3 (0·00–8460·00)
Prevalence of *A lumbricoides* infection at screening	112 (61%)	115 (62%)
Hookworms at screening (eggs per g)*	0·00 (0·00–23·33)	0·00 (0·00–23·33)
Prevalence of hookworm infection at screening	61 (33%)	72 (39%)
Trichuris trichiura at screening (eggs per g)*	83·33 (5·00–295·00)	101·7 (16·67–306.67)
Prevalence of *T trichiura* infection at screening	146 (79%)	153 (82%)
History of any obstetrical complication	28 (15%)	31 (17%)
Number of previous pregnancies		
1–5	151 (82%)	141 (76%)
6–10	32 (17%)	45 (24%)
11+	1 (1%)	0

Data are n (%), mean (SD), or median (IQR). *Parasitological results before treatment as determined by Kato-Katz and reported as eggs per g of stool.

Table 1: **Baseline characteristics of study sample by treatment allocation**

Results

Of 2637 women screened for eligibility between Aug 13, 2007, and Dec 3, 2012, the primary reasons for exclusion were: not infected with *S japonicum* (n=2046) and ultrasound not consistent with viable intrauterine, singleton pregnancy at 12–16 weeks gestation (n=139). Of 370 pregnant women enrolled and randomly assigned, there were five fetal deaths in utero. Birthweight was ascertained for 361 (99%) of 365 live births (figure).

The randomised cohort included 334 (90%) women with low-intensity infection. Table 1 presents baseline socio-demographic, obstetrical, nutritional, and clinical covariates by treatment allocation. These variables were equally distributed between treatment groups.

Treatment with praziquantel did not have a significant effect on the primary outcome, birthweight (2·85 kg in both praziquantel and placebo groups; p=0·988), or secondary efficacy outcomes including prevalence of low birthweight and small for gestational age newborns (table 2). The estimated association of treatment with birthweight (kg) from the mixed-effects model was β=–0·002 (95% CI –0·088 to 0·083; p=0·962). In mixed models of outcomes other than birthweight, covariance parameter estimates for the village and municipality random effects were not significantly different from zero, indicating that reported bivariate comparisons in table 2 are sufficient for these data.

With respect to maternal nutritional status, treatment with praziquantel did not affect maternal weight gain or change in thigh circumference (table 2). At 32 weeks gestation, the group that received praziquantel had significantly higher ferritin but there was no significant difference in maternal haemoglobin at 32 weeks gestation. There was no significant difference between groups in hepcidin, the principal regulator of systemic iron homoeostasis (table 2). No significant differences were recorded between groups with respect to inflammatory markers such as C-reactive protein, tumour necrosis factor α, and interleukin 6. In both groups, all women (100%) reported taking prenatal vitamins with iron as directed.

Treatment was effective at reducing maternal intensity of infection as shown by a significantly higher proportion of women with more than 90% reduction in eggs per g (85% *vs* 50%; p<0·0001). Praziquantel had a significant effect on cure rate as defined by the percentage of women who were not infected with *S japonicum* at 22 weeks gestation (84% *vs* 46%; p<0·0001). Praziquantel treatment had no effect on the prevalence or intensity of the soil-transmitted helminth infections, in particular hookworm. There was also a difference between groups in the percent change in *S japonicum* (eggs per g) from screening to 22 weeks gestation, though this did not reach statistical significance (–53·11 *vs* 128·74; p=0·054).

	Placebo (n=184)	Praziquantel (n=186)	Difference or OR (95% CI)*	p value
Newborn outcomes				
Birthweight (kg)†	2·85 (0·39)	2·85 (0·44)	0·00 (–0·09 to 0·09)	0·988
Low birthweight (<2·5 kg)‡	23 (12·71%)	29 (16·11%)	1·32 (0·73 to 2·38)	0·357
Small for gestational age‡	43 (23·76%)	48 (26·67%)	1·17 (0·73 to 1·88)	0·524
Livebirth rate‡	181/183 (99%)	181/183 (99%)	1·00 (0·14 to 7·18)	1·000
Newborn haemoglobin (g/dL)†	17·33 (2·48)	17·50 (2·33)	0·16 (–0·34 to 0·66)	0·521
Newborn serum transferrin receptor, heel stick (ng/mL)§	0·000 (0 to 3·7)	0·000 (0 to 0)	0 (0 to 0)	0·068
Newborn ferritin, heel stick (ng/mL)§	313·7 (211·2 to 402·1)	289·4 (215·0 to 408·7)	–3·96 (–35·88 to 28·00)	0·818
Newborn serum transferrin receptor:ferritin ratio, heel stick§	0 (0 to 0·01)	0 (0 to 0)	0 (0 to 0)	0·070
Maternal outcomes				
Maternal haemoglobin at 32 weeks gestation (g/dL)†	11·04 (1·30)	11·05 (1·18)	0·013 (–0·24 to 0·27)	0·923
Change in maternal haemoglobin (g/dL)†	–0·42 (1·39)	–0·44 (1·38)	–0·01 (–0·30 to 0·27)	0·926
Maternal ferritin at 32 weeks gestation (ng/mL)§	10·52 (2·75 to 21·97)	14·71 (2·79 to 28·78)	2·54 (0·00 to 5·65)	0·049
Maternal serum transferrin receptor:ferritin ratio at 32 weeks gestation§	0·00 (0 to 27·11)	0·33 (0 to 13·26)	0 (0 to 0)	0·993
Maternal hepcidin (ng/mL)§	2·58 (0·94 to 6·00)	3·38 (1·18 to 5·50)	0·21 (–0·32 to 0·77)	0·439
Maternal weight gain from enrolment to 32 weeks gestation (kg/week)†	0·33 (0·13)	0·32 (0·13)	–0·01 (–0·03 to 0·02)	0·704
Mean change in maternal thigh skin-fold thickness from enrolment to 32 weeks gestation (mm/week)†	0·08 (0·09)	0·08 (0·09)	0·01 (–0·02 to 0·02)	0·517
Treatment success (>90% reduction in egg count from screening to 22 weeks gestation)‡	92/184 (50·0%)	157/184 (85·3%)	5·81 (3·53 to 9·59)	<0·0001
Cure rate (defined as percentage with 0 eggs per g at 22 weeks gestation)‡	85/184 (46·2%)	154/184 (83·7%)	5·98 (3·67 to 9·73)	<0·0001
Percent change in *Schistosoma japonicum* (eggs per g) from screening to 22 weeks gestation†	128·74 (1241·04)	–53·11 (306·71)	–181·9 (–367·7 to 3·95)	0·054

Data are n (%), n/N (%), mean (SD), or median (IQR), unless otherwise indicated. *Difference reported for continuous measures as difference in means or nonparametric Hodges-Lehmann estimate of location shift; odds ratio (OR) reported for categorical measures. †*t* test. ‡χ^2 test. §Wilcoxon 2 sample.

Table 2: **Unadjusted primary and secondary efficacy outcomes by treatment allocation**

	Placebo (n=184)	Praziquantel (n=186)	Difference or OR (95% CI)*	p value
Change in maternal laboratory parameters†				
Creatinine (mg/dL)	0·01 (0·17)	0·07 (0·22)	0·06 (0·02 to 0·10)	0·004
Blood urea nitrogen (mg/dL)	1·22 (6·13)	1·71 (5·25)	0·49 (–0·68 to 1·66)	0·410
Alanine transaminase (U/L)	–1·63 (10·50)	–0·39 (8·42)	1·24 (–0·71 to 3·19)	0·211
Aspartate transaminase (U/L)	–0·96 (9·87)	–0·63 (9·15)	0·33 (–1·62 to 2·28)	0·738
Bilirubin (mg/dL)	–0·10 (0·31)	–0·08 (0·33)	0·02 (–0·05 to 0·08)	0·605
White blood cell count (×10^9/L)	1·25 (1·39)	0·78 (1·85)	–0·47 (–0·81 to –0·14)	0·006
Granulocyte count (×10^9/L)	0·68 (1·39)	0·38 (1·54)	–0·29 (–0·60 to 0·01)	0·062
Lymphocyte count (×10^9/L)	0·49 (0·42)	0·33 (0·51)	–0·16 (–0·26 to –0·06)	0·001
Haemoglobin (g/dL)	–0·23 (0·74)	–0·22 (0·78)	0·01 (–0·15 to 0·16)	0·921
Platelets (×10^9/L)	9·81 (50·73)	2·90 (40·74)	–6·91 (–16·34 to 2·52)	0·150
Clinical endpoints				
Serious adverse events (maternal)	16 (9%)	18 (10%)	1·13 (0·56 to 2·28)	0·74
Serious adverse events associated with treatment (maternal)	0	0	..	1·00
Maternal seizure within 24 h of treatment	0	0	..	1·00
Any severe adverse reaction within 24 h of treatment	2 (1%)	5 (3%)	2·51 (0·40 to 26·66)	0·45
Serious adverse events (infant)§	18 (10%)	27 (15%)	1·59 (0·84 to 3·00)	0·15
Serious adverse events associated with treatment (infant)	0	0	..	1·00
Abortion (fetal loss between treatment and 20 weeks gestation)	0	0	..	1·00
Fetal death in utero‡	1 (1%)	2 (1%)	1·99 (0·10 to 117·98)	1·00
Newborn not healthy‡¶	12 (7%)	12 (7%)	1·00 (0·44 to 2·29)	1·00
Congenital anomaly§	2 (1%)	3 (2%)	1·51 (0·17 to 18·24)	1·00

Data are n (%) or mean (SD), unless otherwise indicated. *Difference reported for continuous measures as difference in means or non-parametric Hodges-Lehmann estimate of location shift; odds ratio (OR) reported for categorical measures. †Change measures calculated as follow-up measure minus initial measure; *t* test. ‡χ^2 test or Fisher's exact test. §Among 362 livebirths. ¶Among 366 assessed deliveries.

Table 3: **Laboratory and clinical safety endpoints by treatment allocation**

With respect to other secondary efficacy outcomes for newborns, maternal treatment did not affect newborn haemoglobin level or ferritin (table 2). Non-significant differences were noted for newborn sTfR and sTfR-to-ferritin ratios; newborns of mothers treated with praziquantel had slightly lower concentrations of both biomarkers, potentially showing less cellular iron thirst and greater total body iron, respectively, among newborns of treated versus untreated mothers (table 2).

No significant changes in serum chemistries or haematological parameters were recorded in mothers before and 24 h after dosing, with the following exceptions. Change in white blood cell counts and lymphocyte counts were significantly different with women in the placebo group having a greater increase from pre-treatment to post-treatment (table 3). Women in the praziquantel group had a significantly higher change in creatinine from pre-dosing to post-dosing compared with the placebo group (0·07 mg/dL *vs* 0·01 mg/dL; p=0·004); however, these were all mild (grade I) elevations.

Overall, 18 participants in the praziquantel group and 16 in the placebo group had a serious adverse event with a wide range of event classifications that were largely expected during pregnancy in a population at high risk of adverse pregnancy outcomes. None occurred in the immediate post-treatment period. There were no significant differences in the rate of fetal death in utero, the livebirth rate, or the number of congenital anomalies (table 3). Congenital anomalies included two newborns (one in each treatment group) with talipes equinovarus (club feet) and three infants with cleft lip or palate (two in the praziquantel group, one in the placebo group).

With respect to immediate reactogenicity, 323 participants, 169 of whom received praziquantel, reported at least one side-effect of treatment that was of mild or greater severity. Reactions graded as severe occurred in five patients in the praziquantel group and two in the placebo and included headache, fever, and malaise. All severe reactions were attributed to study drug administration and resolved during the 14 day reactogenicity period.

Discussion

This is the first clinical trial to investigate the efficacy and safety of treating pregnant women with *S japonicum* infection at the higher dose of praziquantel (60 mg/kg) recommended for Asian schistosomiasis. The study was a phase 2 trial designed to assess the effect on pregnancy outcomes and collect initial toxicology data for both mother and newborn. Treatment did not have a significant effect on the primary outcome, birthweight, or the rate of low birthweight newborns. Treatment might have led to improved iron status in both the

mother at 32 weeks gestation and the newborn. Importantly, praziquantel was well tolerated with rates of immediate reactogenicity similar in this cohort of pregnant women to those seen in non-pregnant participants.[13] Additionally, there were no significant differences in the rates of serious adverse events among mothers or newborns, comparing the treated with untreated groups.

This trial differs from another important four-group randomly assigned controlled trial done in an *S mansoni* endemic region of Uganda. In that study, women were randomly assigned to receive either albendazole plus praziquantel, albendazole alone, praziquantel alone, or placebo. All women were randomly assigned to one of the four groups, whether or not they harboured specific baseline infections with soil-transmitted helminths or *S mansoni*.[24] The mean gestational age at enrolment was 26·6 weeks. Neither the Ugandan study, which treated women later in gestation, nor our trial, which randomised women early in the second trimester, shows a significant effect on birthweight. In the Ugandan study, this was true even when analyses were restricted to women found to be infected with *S mansoni*. In both studies of the women who were infected, most had low-intensity infections. In the present study, interactions between baseline intensity of infection and treatment effect on birthweight were also not significant, suggesting that there were no differences in treatment efficacy among women with moderate-intensity or high-intensity infections. However, this should be interpreted with caution due to the small number of women with moderate-intensity and high-intensity infections enrolled (36 [10%] of 370 at baseline).

Other explanations for lack of effect on birthweight include the fact that treatment did not significantly affect maternal weight gain, a hypothesised potential mechanism. This result might be due, in part, to a lack of effect on maternal inflammation even by 32 weeks gestation. In previous observational studies done by our group, women infected with *S japonicum* had significantly higher tumour necrosis factor α concentrations at 32 weeks gestation (mean 2·11 pg/mL) than uninfected women (mean 0·34 pg/mL).[32] In the trial, these values at 32 weeks gestation were 1·6 pg/mL and 1·3 pg/mL for the placebo and praziquantel group, respectively, suggesting that treatment did not resolve inflammation. Another hypothesised mechanism through which praziquantel could lead to improved birthweight was through effects on placental health. Observational studies from our group suggest that infection with *S japonicum* culminates in a pro-inflammatory signature at the maternal–fetal interface and this is associated with lower birthweight.[32] Further, schistosome antigens elicit a pro-inflammatory immune response from primary human trophoblast cells from healthy placentas.[33] However, praziquantel given during gestation might not sufficiently disrupt the delivery of immunogenic schistosome antigens to the placenta, given that treatment results in a period of increased circulating antigens with a prolonged inflammatory immune response.[8,34] It remains possible that schistosome infections adversely affect placental health, but treatment after the first trimester might not mitigate this risk.

Additionally, neither our study nor the Ugandan trial showed a significant effect on maternal haemoglobin or prevalence of maternal anaemia. In studies done by our group in non-pregnant participants, we have shown a significant time lag after treatment before improvements in haemoglobin are noted, with no significant difference noted 3 months after therapy, but a significant increase 6 months after treatment.[8] We did find that women treated with praziquantel had significantly higher ferritin concentrations at 32 weeks gestation. Additionally, there was a trend toward increased newborn iron endowment as captured by the sTfR-to-ferritin ratio, a marker for total body iron, and sTfR, a marker of cellular iron thirst among their newborns. It is likely that treatment began to modify the risk of maternal anaemia of inflammation, which would be expected to increase iron absorption from the gut and increase the pool of maternal bioavailable iron before an effect on maternal haemoglobin could be seen.[35]

Both the Ugandan study and our study did not record significant differences in the rate of congenital anomalies or other serious adverse events comparing the praziquantel and placebo groups. Our study additionally captured abortion, defined as fetal loss occurring before 20 weeks gestation, which in this case would have been within 4–8 weeks of praziquantel dosing. There were no differences between groups in either abortion or rates of fetal death in utero at any point in gestation. Taken together, these studies contribute key toxicology data about the use of praziquantel during human pregnancy, supporting its safety at different timepoints during pregnancy after 12 weeks gestation.

WHO guidelines from 2002 and 2006 recommend that all schistosomiasis-infected pregnant and lactating women be considered high-risk groups and be offered treatment with praziquantel individually or during treatment campaigns.[5–7] These recommendations were based on safety from animal studies and inadvertent exposures during human pregnancy, rather than data from controlled trials in human beings. As such, the recommendations did not provide conclusive data regarding safety and, due in part to this constraint, many schistosomiasis endemic regions continue to exclude pregnant and lactating women from both mass drug administration and individualised treatment programmes. Results from this study, together with the Ugandan study, should provide necessary reassurance that praziquantel given after 12 weeks gestation is safe, effectively treats schistosomiasis, and might improve both maternal and newborn iron status.

Study limitations include the low number of women who had moderate-intensity or high-intensity infections

who might have been more likely to experience schistosomiasis-associated morbidity and benefit from treatment. This limitation restricts our ability to understand the effect of treatment in the context of high-intensity infections. We were also surprised to find that 85 (46%) of 184 women in the placebo group were cured by 22 weeks gestation. This result is unlikely to be due to treatment outside of the study because it was the strict policy of the Philippines Department of Health to withhold treatment from pregnant women and almost all treatment occurs during mass drug administration campaigns. Further, all women in both groups provided three stools at follow-up for assessment. It is more likely that many women in the placebo group with light-intensity infections at baseline might have been missed at 22 weeks gestation, contributing to an apparently high rate of cure. Additionally, by design, our study sample consisted of otherwise healthy, adult women, restricting the generalisability of findings somewhat. In many parts of the world mass drug administration is the current approach to schistosomiasis control, whereas women in this study had to be infected with *S japonicum* to participate. Given the use of single dosing in mass drug administration campaigns as opposed to the split dose employed, reactogenicity in practice might be higher than recorded in this trial. Finally, in the context of inflammation, ferritin is raised, thus complicating its interpretation as a measure of stored iron. Therefore, it is possible that women treated with praziquantel had higher concentrations of ferritin at 32 weeks gestation due to prolonged inflammation after treatment. This explanation is unlikely given the expectation that acute phase responses such as raised ferritin would resolve 4–5 months after treatment and is further evidenced by a lack of difference in other acute phase proteins such as C-reactive protein.

Results from this trial provide important data from a controlled trial in support of the expansion of treatment policies to include pregnant women as recommended by WHO. Though this study was not powered to detect differences in rates of rare outcomes such as congenital anomalies, these results, together with results from the Ugandan study, post-marketing surveillance data including experience from treating pregnant women in mass drug administration campaigns in some African nations, and data from animal studies support ending the exclusion of pregnant women from mass drug administration campaigns and individualised treatment. Though we did not record an effect on birthweight, based on animal models and human observational and mechanistic studies, schistosomiasis could possibly adversely affect pregnancy outcomes; however, treatment during gestation could be too late to have an effect. If this is the case, including pregnant women in mass drug administration campaigns will increase the likelihood that they enter subsequent pregnancies free of schistosomiaisis infection.

Contributors

RMO, LPA, VT, AI, PIB, JDK, HWW, and JFF participated in the study planning and design. RMO, LPA, VT, PIB, JLSL, GGE, EBA, DBSM, and AI participated in data collection. RMO participated in data interpretation. NW did the data analyses. JFF and EAM participated in the literature review and primary manuscript writing. JDK and HWW did the laboratory assays.

Declaration of interests

We declare no competing interests.

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References

1 Anon. Schistosomiasis: number of people treated in 2009. *Wkly Epidemiol Rec* 2011; **86:** 73–80.
2 WHO. Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions. Geneva: World Health Organization, 2006.
3 Frohberg H. The toxicological profile of praziquantel in comparison to other anthelminthic drugs. *Acta Leiden* 1989; **57:** 201–15.
4 Ni YC, Shao BR, Zhan CQ, Xu YQ, Ha SH, Jiao PY. Mutagenic and teratogenic effects of anti-schistosomal praziquantel. *Chin Med J* 1982; **95:** 494–98.
5 Olds GR. Administration of praziquantel to pregnant and lactating women. *Acta Trop* 2003; **6:** 185–95.
6 WHO. Report of the WHO informal consultation on the use of praziquantel during pregnancy lactation and albendazole/mebendazole in children under 24 months. Geneva: World Health Organization, 2002.
7 Allen HE, Crompton DW, de Silva N, LoVerde PT, Olds GR. New policies for using anthelmintics in high risk groups. *Trends Parasitol* 2002; **18:** 381–82.
8 Coutinho HM, Acosta LP, McGarvey ST, et al. Nutritional status improves after treatment of *Schistosoma japonicum*-infected children and adolescents. *J Nutr* 2006; **136:** 183–88.
9 Coutinho HM, McGarvey ST, Acosta LP, et al. Nutritional status and serum cytokine profiles in children, adolescents, and young adults with *Schistosoma japonicum*-associated hepatic fibrosis, in Leyte, Philippines. *J Infect Dis* 2005; **192:** 528–36.
10 Friedman JF, Kanzaria HK, Acosta LP, et al. Relationship between *Schistosoma japonicum* and nutritional status among children and young adults in Leyte, the Philippines. *Am J Trop Med Hyg* 2005; **72:** 527–33.
11 McGarvey ST, Aligui G, Daniel BL, Peters P, Olveda R, Olds GR. Child growth and schistosomiasis japonica in northeastern Leyte, the Philippines: cross-sectional results. *Am J Trop Med Hyg* 1992; **46:** 571–81.
12 McGarvey ST, Aligui G, Graham KK, Peters P, Olds GR, Olveda R. *Schistosomiasis japonica* and childhood nutritional status in northeastern Leyte, the Philippines: a randomized trial of praziquantel versus placebo. *Am J Trop Med Hyg* 1996; **54:** 498–502.
13 Olds GR, King C, Hewlett J, et al. Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. *J Infect Dis* 1999; **179:** 996–1003.
14 McGarvey ST, Wu G, Zhang S, et al. Child growth, nutritional status, and schistosomiasis japonica in Jiangxi, People's Republic of China. *Am J Trop Med Hyg* 1993; **48:** 547–53.

15 Latham MC, Stephenson LS, Kurz KM, Kinoti SN. Metrifonate or praziquantel treatment improves physical fitness and appetite of Kenyan schoolboys with *Schistosoma haematobium* and hookworm infections. *Am J Trop Med Hyg* 1990; **43:** 170–79.

16 Coutinho HM, Leenstra T, Acosta LP, et al. Pro-inflammatory cytokines and C-reactive protein are associated with undernutrition in the context of *Schistosoma japonicum* infection. *Am J Trop Med Hyg* 2006; **75:** 720–26.

17 Leenstra T, Acosta LP, Langdon GC, et al. *Schistosomiasis japonica*, anemia, and iron status in children, adolescents, and young adults in Leyte, Philippines. *Am J Clin Nutr* 2006; **83:** 371–79.

18 Leenstra T, Coutinho HM, Acosta LP, et al. *Schistosoma japonicum* reinfection after praziquantel treatment causes anemia associated with inflammation. *Infect Immun* 2006; **74:** 6398–407.

19 Kanzaria HK, Acosta LP, Langdon GC, et al. *Schistosoma japonicum* and occult blood loss in endemic villages in Leyte, the Philippines. *Am J Trop Med Hyg* 2005; **72:** 115–18.

20 Bustinduy AL, Sousa-Figueiredo JC, Adriko M, et al. Fecal occult blood and fecal calprotectin as point-of-care markers of intestinal morbidity in Ugandan children with *Schistosoma mansoni* infection. *PLoS Negl Trop Dis* 2013; **7:** e2542.

21 Ndamba J, Makaza N, Kaondera KC, Munjoma M. Morbidity due to *Schistosoma mansoni* among sugar-cane cutters in Zimbabwe. *Int J Epidemiol* 1991; **20:** 787–95.

22 Betson M, Sousa-Figueiredo JC, Kabatereine NB, Stothard JR. Use of fecal occult blood tests as epidemiologic indicators of morbidity associated with intestinal schistosomiasis during preventive chemotherapy in young children. *Am J Trop Med Hyg* 2012; **87:** 694–700.

23 Qunhua L, Jiawen Z, Bozhao L, et al. Investigation of association between female genital tract diseases and *Schistosomiasis japonica* infection. *Acta Trop* 2000; **77:** 179–83.

24 Ndibazza J, Muhangi L, Akishule D, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. *Clin Infect Dis* 2010; **50:** 531–40.

25 United States Agency for International Development. United States Agency for International Development country health statistical report for 2005: Philippines. 2008. Washington, DC: USAID. http://pdf.usaid.gov/pdf_docs/Pnadm408.pdf (accessed Sept 1, 2008).

26 WHO. Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study. *Bull World Health Organ* 1995; **73** (suppl): 1–98.

27 Villar J, Cogswell M, Kestler E, Castillo P, Menendez R, Repke JT. Effect of fat and fat-free mass deposition during pregnancy on birth weight. *Am J Obstet Gynecol* 1992; **167:** 1344–52.

28 Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. *J Pediatr* 1979; **95** (5 pt 1)**:** 769–74.

29 Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. *Obstet Gynecol* 1982; **59:** 624–32.

30 Ezeamama AE, Friedman JF, Acosta LP, et al. Helminth infection and cognitive impairment among Filipino children. *Am J Trop Med Hyg* 2005; **72:** 540–48.

31 Filmer D, Pritchett LH. Estimating wealth effects without expenditure data—or tears: an application to educational enrollments in states of India. *Demography* 2001; **38:** 115–32.

32 Kurtis JD, Higashi A, Wu HW, et al. Maternal *Schistosomiasis japonica* is associated with maternal, placental, and fetal inflammation. *Infect Immun* 2011; **79:** 1254–61.

33 McDonald EA, Kurtis JD, Acosta L, et al. Schistosome egg antigens elicit a proinflammatory response by trophoblast cells of the human placenta. *Infect Immun* 2013; **81:** 704–12.

34 Hassan MM, Medhat A, Makhlouf MM, et al. Detection of circulating antigens in patients with active *Schistosoma haematobium* infection. *Am J Trop Med Hyg* 1998; **59:** 295–301.

35 Lewis SM, Bain B, Bates I. Dacie and Lewis practical haematology, 10th edn. Philadelphia, PA: Churchill Livingstone, 2006.