COST-EFFECTIVENESS ANALYSIS OF THE IMPACTS ON INFECTION AND MORBIDITY ATTRIBUTABLE TO THREE CHEMOTHERAPY SCHEMES AGAINST *SCHISTOSOMA JAPONICUM* IN HYPERENDEMIC AREAS OF THE DONGTING LAKE REGION, CHINA

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Abstract. A study was carried out in 8 villages endemic with *S. japonicum* in Hunan Province, China from 1998 to 2000 to evaluate the cost-effectiveness in preventing schistosome infection and related morbidity under three chemotherapy schemes: (1) 'clue' chemotherapy, consisting of treatment to those with contact with infected water and/or symptoms of infection; (2) 'mass' chemotherapy-treatment to all the villagers except those not able to take praziquantel; and (3) 'screen' chemotherapy–treatment prescribed to the stool egg positive cases after Kato-Katz examination. An itemized cost menu was used to estimate the cost incurred to each scheme, from the perspective of the health care provider. The numbers of cases prevented by chemotherapy schemes were estimated through standardized attributable fractions of the outcomes to absence of chemotherapy before intervention. The cost-effectiveness ratios were calculated using weighted ranks of unit costs of the four outcome measurements: the costs per case with infection, liver and spleen abnormality (as determined by ultrasonography) prevented and 1% reduction in intensity of infection (as estimated by egg per gram feces, EPG) after the two years of intervention. Sensitivity of total cost to changes in the costs of personnel, praziquantel and other key factors were analyzed. It is demonstrated that all the three schemes had a significant impacts on the prevalence and intensity of infection, but the overall effects on liver and spleen morbidity of the residents varied between schemes. Mass chemotherapy achieved the best cost-effectiveness ratio, with unit costs of preventing cases of infection, liver and spleen abnormality and 1% reduction of EPG being RMB yuan 161.2, 99.8, 219.3 and 176.3, respectively. However, clue and screen chemotherapy schemes did not show significant prevention of liver damages in the villagers. The unit costs per case prevented for the outcomes were RMB yuan 140.2, 602.7 and 169.3, respectively for clue chemotherapy, while RMB yuan 190.0, 448.4 and 145.0 respectively for screen chemotherapy. The study concluded that mass chemotherapy should still be the choice of preference in areas where prevalence of infection and frequencies of contact with infested water by residents are high, particularly if the drug cost could be further reduced. Clue chemotherapy could be an alternative to mass chemotherapy, especially when the frequency of water contact is not as high as 80% recorded in our study. Screen chemotherapy is the least favored option in the hyperendemic area of Hunan Province.

INTRODUCTION

Schistosomiasis is a parasitic disease of significant public health importance in developing countries. Among human parasitic diseases, schistosomiasis ranks second behind

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malaria in terms of socio-economic and public health importance in tropical and subtropical areas (WHO, 2000). The disease is endemic in 74 developing countries, infecting more than 200 million people in rural agricultural and peri-urban areas. In the lower and middle reaches of the Yangtze River valley in China, schistosomiasis japonica is one of the top public health concerns. Currently, this parasitic zoonosis is still not under effective control in the five provinces in the lake region and two provinces in the mountainous region of China, *ie*, Hunan, Hubei, Jiangxi, Anhui, Jiagnsu, Yunnan and Sichuan (Zhou *et al*, 1994; Ross *et al*, 1997; Zheng and Feng, 2000). Dongting Lake region of Hunan Province is one of the most affected areas for the disease in China. Prevalence and morbidity of infection are still quite high in some of the hyperendemic areas of the region, for example, in a 1995 survey in the lake-beach endemic area, a 22.51% of stool egg positive prevalence proportion was recorded (Yu *et al*, 1999; Li *et al*, 1997).

Chemotherapy is currently the mainstay control strategy in the schistosomiasis endemic countries, and is designed to reduce and control the morbidity levels among the affected population (WHO, 1993). It is well proved that chemotherapy with praziquantel is effective in reducing both the prevalence of schistosome infection and related morbidity in the region (Li *et al*, 1997; Ross *et al*, 1998). Recent studies show that *S. japonicum* strains remains highly susceptible to praziquantel, though mass chemotherapy has been applied extensively in the region for more than 14 years (Liang *et al*, 2001; Yu *et al*, 2001). Moreover, the price of praziquantel is decreasing due to expiration of patent (Doenhoff *et al*, 2000). There are a number of schemes available to administer praziquantel chemotherapy to the community level, such as mass, screen and selective chemotherapy depending on the epidemiological situation. In the absence of information on the relative cost-effectiveness of alternative chemotherapy schemes, the question this present study faced was how we could deliver the drug to the community in a more efficient way, given the limited resources available. This question is most pressing for those areas where mass chemotherapy has been implemented for years in the hyperendemic areas of schistosomiasis in China.

Economic evaluations on schistosomiasis control project are limited. And only few studies are available on schistosomiasis japonica, and these are predominantly in Chinese (Jiang *et al*, 1999; Lin *et al*, 2000; Liu *et al*, 2000; Qiu *et al*, 2000; Wen *et al*, 2000; Yun *et al*, 2000). The outcome measurements used in most studies, such as percentage reduction in prevalence and number of infections reduced after the intervention, are not enough to comprehensively reflect the overall impact of control measures, in view of the current strategy to control the morbidity of the infection. The objectives of this study are to evaluate the impacts on morbidity and the cost-effectiveness of alternative chemotherapy schemes, through introducing ‘impact fractions’ to estimate the overall effects. These estimations of the impact on morbidity would be more relevant to the objectives of current strategy (Guyatt and Tanner, 1996). The study was carried out during 1998 to 2000 in the Dongting Lake region of Hunan Province, China.

METHODS

This is a quasi-experimental study, involving two cross-sectional surveys in 8 study villages where different chemotherapy schemes were carried out, one before the intervention as the baseline survey and one six months after the second year chemotherapy intervention as the evaluation survey. The three chemotherapy schemes were randomly allocated to the study villages by the investigators.

The study settings

The Dongting Lake is one of the largest freshwater lakes in China, second only to Poyang Lake of Jiangxi Province. It is a water storage lake, receiving water from four branch rivers, *ie*, Xiang, Zi, Yuan and Li Rivers in the upper reaches, and discharges into the Yangtze River through four outgoing rivers. Historically the lake was much larger than the present size, reaching an area greater than 6,000 km^2. However, the lake is currently shrinking due to the silt deposits from the upper reaches and the Yangtze River during the flooding season. According to the data from the year 1951 to 1983, the total silt deposited into the lake bed from the four branch rivers and the Yangtze River was about 3.3 billion m^3 (Anonymous, 1990; Tian, 1990). The direct consequence of silt deposition is the shrinkage of the lake area and decrease of water storage function in the flooding season, leading to the more frequent occurrences of serious flooding year by year. The current area of the lake is 2,691 km^2.

The Dongting Lake region refers to the plains and surrounding areas centered by the lake and its branch rivers, covering an area of 32,064 km^2 and accounting for 15.1% of the total area of Hunan Province. It is located in the subtropical area with temperate climate and abundant rainfall. The total population in the region is about 12 million, about 20% of that of the province. Most residents of the lake regions live inside huge embankments measuring 3,471 km, which protect the residents from flooding. Outside of the embankment are the huge areas of lake water and beaches, most of which are flooded in the flooding season but they are accessible in the autumn, winter and early spring. There are many types of vegetations along the lake beaches, including grass, weeds and wave protection forests. The lake beaches serve as ideal habitat for the growth and reproduction of the *Oncomelania* snails, the intermediate host of schistosome. The region is one of the most important agriculture bases both for the province and the country, producing a range of products such as rice, cotton, tea, and aquatic products.

The study villages and population

The study was carried out in 8 farming villages of the "lake-embankment" type endemic area (Yu *et al*, 1999), two each in the western and southern regions, and 4 in the eastern Dongting Lake regions (Fig 1). These villages were selected from a list based on the epidemiological and socio-economic situations of the region, and convenience with respect to conducting research work was also a factor taken into consideration. The villages were similar in endemicity of *S. japonicum* infection and socio-economic factors, typical and representative in the hyperendemic area (prevalence about 15%, according to the classification of Ministry of Health, China) in the area based on the disease surveillance data of the World Bank Loan Schistosomiasis Control Program in the province (Chen *et al*, 1998). In terms of employment, villagers are mainly engaged in the production of grain and cotton, while some take up fishing in their spare time. The living areas are distributed along the inside of the embankment, next to which are large areas of transmission sites where *O. hupensis hupensis*, the intermediate snail host of the parasite, thrives. The residents get infected predominantly in the lake/river outside the embankment through daily activities like washing clothes in the lake/river, swimming, and production activities such as fishing, cutting grass for fertilizer (Wu *et al*, 1993). Transmission usually occurs during April to November although there are two distinct

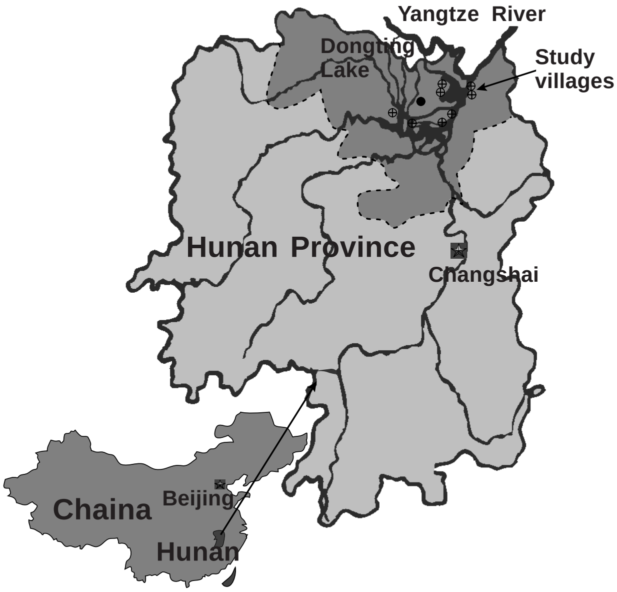

Fig 1–Location of the study villages in Hunan Province, China.

transmission peaks during this period: one from April to May when flooding begins, and the other from September to November while flooding is receding. Malaria is non-endemic in this region (Wu *et al*, 1993).

Villagers in the villages aged 3-65 years old were included as the study population, to whom different chemotherapy schemes were administered during 1998 to 2000.

The intervention

Three mainstay chemotherapy schedules currently being recommended and used in the endemic areas in China were implemented in the three groups of pilot villages.

Clue chemotherapy (Group A): The so-called 'clue' chemotherapy aims to identify high risk groups to administer praziquantel chemotherapy through a simple questionnaire interview of the individuals inquiring about the history related to schistosome infection. The staff from the township anti-schistosomiasis stations visited the endemic villages in the spring/summer time before the annual flood to determine the subjects for treatment. Those with history of water contact in the past year and/or schistosomiasis related symptoms in the past two months were regarded as the subjects of treatment and administered with a single dose of praziquantel at the dosage of 40 mg/kg (maximum dosage 2,400 mg for one person), and for those body weight less than 30 kg, a dosage of 45 mg/kg was given.

Mass chemotherapy (Group B): All the villagers aged 3-65 years old in the selected villages were given a single dose of praziquantel at the same dosage as clue chemotherapy, except for those with severe heart, liver, or kidney problems and the pregnant women. The work was undertaken by mobile chemotherapy teams from the local schistosomiasis stations before the annual flooding, with required coverage of 80% to the target population.

Screen chemotherapy (Group C): The villagers were screened by Kato-Katz examination of a single stool with 3 slides. The staff of the anti-schistosomiasis stations went to the villages and undertook stool examination in the village site. Those subjects with positive stool egg samples were then administered with a single dose of praziquantel for treatment at the same dosage and time as clue chemotherapy.

Evaluation/observation

Selection of subjects for evaluation: A random cluster sampling procedure was used to select subjects from the study population for the purpose of this evaluation. An administrative village (formerly "brigade" in Mao's time) is the lowest government unit under the township (formerly "commune") level in the countryside in China. There are a number of residential clusters (formerly "production team") in a village, usually consisting of about 10 to 15 persons depending on the situation, in one administrative village. The residential clusters were the unit for sampling. Firstly, the list of residential clusters of each selected village was obtained from the local anti-schistosomiasis stations. Second, about 2-3 residential clusters were randomly chosen from each village, with numbers of residents between 350-500 depending on the size of population of each residential cluster. After the selection of groups was done, rosters of the residential clusters were obtained from the village administration authorities. All the villagers aged 3-65 years in the selected residential clusters were then recruited as the subjects for evaluation. For clue and mass chemotherapy groups, about 100 additional school children aged 7-12 years were chosen from the corresponding primary schools of the village, initially intended to increase the number of younger age groups who were thought to be the high risk groups of schistosome infection.

Ethical clearance for the study was obtained from the Hunan Institute of Parasitic Diseases. The village heads and villagers were explained the purpose and benefits of the study, and a written informed consent was obtained from each family with study subjects. All the examinations and praziquantel were free to the subjects, and immediate treatments were given to any side effects arising from taking the drug.

Interview: Separate interviews for the purposes of evaluation were undertaken by one investigator together with one staff from the local anti-schistosomiasis station. All the study subjects were interviewed face-to-face both at baseline and evaluation, and children younger than 12 were accompanied by their parents. Information collected included personal data, abdominal pain and diarrhea (three or more times a day, and/or with bloody stool) in the past two months, and contact with water outside the embankment in the past year.

Ultrasound examination: Ultrasonographic examinations were carried out on all subjects. The same group of ultrasonographers from the Hunan Institute of Parasitic Diseases or the local anti-schistosomiasis stations undertook the examinations in the same villages before and after the intervention with portable Shimadzu or Hitachi EUB-200 scanners using the linear transducers at 3.5 MHz. All the observers were briefed ahead of the field work and asked to follow the unified protocol in all the measurements, but were not blind to the intervention. Each subject was observed by two examiners, and discussions were held to reach a consensus where there was any disagreement. Reporting and categorizations of liver and spleen abnormality were made following the Cairo protocol in combination with Chinese references (TDR/WHO, 1993; Zhou and Guo, 1998). For liver scanning, those with grade II and/or above parenchymal changes and/or with left liver enlargement (longitudinal length > 80 mm of the whole, or >30 mm below the mid-sternal line, or thickness > 70 mm) are classified as abnormal, and otherwise as normal. For spleen measurement, length ≤ 120 mm or transverse section ≤ 40 mm are classified as normal, and otherwise as abnormal.

Parasitological examination: All the subjects were required to submit an ample amount of stool specimen. For each specimen, 3 Kato-Katz slides were prepared, after being sieved and calibrated by means of a nylon wire mesh and 41.7 mg plastic templates. Dissolution of particulate matter was accomplished by overlaying the stool with a green cellophane coverslip previously soaked in glycerine and malachite green stain for 24 hours. Slides were read 24 hours after their initial preparation by two experienced laboratory technicians to determine number of eggs per gram of stool. Consensus had to be reached between two technicians for diagnosis regarding suspicious schistosome eggs. Ten percent of the slides were randomly checked by a third microscopist for accuracy of reading. Eggs per gram feces (epg) were calculated from the total number of eggs of the 3 slides multiplied by factor 8.

Collection and measurement of cost data: Only the costs of the intervention were included in this study, whereas those research costs which would not be incurred if any of the interventions were scaled up (such as ultrasound) were not included. A detailed record form was developed for cost data collection, on which the inputs of personnel, materials and equipment were recorded in detail. Using an itemized cost menu, the cost of each scheme was calculated. The cost menu was designed based on the actual inputs for different activities and where the data were missing expert guesses were made based on values reported in the literature.

Personnel: Personnel involved included supervisors, medical officers, laboratory technicians and medical assistants. The salary and per diem were estimated based on the average of the county level anti-schistosomiasis station in the province, and training cost of the trainers and trainees were included.

Consumables: For the praziquantel tablet (20 mg) currently being used in China, an average 10 tablets per dose was assumed considering both adults (maximum 12 tablets) and children. Given that the purchasing price was RMB yuan 0.23 per tablet including transport and customs cost, with an additional 10% of wastage, the unit cost was therefore RMB yuan 2.53 per dose. Other drugs were used for treating side effects arising from praziquantel. One third of those receiving praziquantel treatment were assumed needing treatment, at 1 yuan per dosage plusing 10% wastage. Slides, Kato plates, detergent and disinfectant, and others were all materials for stool examination. They were calculated based on the actual consumption for each examination. Forms and stationary were used for recoding the results of survey and treatment, and other paper work for the project.

Vehicle: The average cost of renting a mini bus (6 seats) from the market was used. As this figure varied from one place to the other, an average rental per day in the middle economic township level was used. The rental included the basic price (including the salary of the owner), and a running cost was added per kilometer covered.

Capital: Microscopes were used for reading slides in stool examination. Here we assume the current replacement cost of a microscope was 3,500 yuan, with a life expectancy of 10 years and a discount rate of 10%. The annualization factor was thus 6.145 (Creese and Paker, 1994), and the yearly cost 570 yuan. We further assumed that 100 working days was used in a year. The cost per working day was therefore 5.7 yuan. Also, a weighing scale was used to weigh the subject to calculate the dosage of praziquantel. Assuming a replacement cost of 250 yuan, life expectancy of 2 years (annualization factor 1.736), and 50 useful working days a year, the average cost per working day was 2.88 yuan. Bicycles were used for transportation to and from the endemic village and the anti-schistosomiasis station by the local staff. Assuming a replacement cost of 350 yuan, a life expectancy of 3 years (annualization factor 2.487), and 100 useful working day in a year, the average cost per working day was thus 1.41 yuan.

Data processing and analysis

All the data were checked for consistency and accuracy before coding and entering in the computer. Epi Info 2000 (CDC/WHO, 2000) was used to establish the data structure, enter data and make the calculations. Statistical Package for Social Science 10.0 (SPSS 10.0, SPSS Inc, 1999) and Excel 2000 (Microsoft, 2000) were used for descriptive, inferential and cost analysis.

Prevalence of *S. japonicum* infection and morbidity indicators were standardized using single combined population of the three groups at baseline as the standard. Eggs per gram feces (EPG) was used to estimate intensity of infection, and both the arithmetic mean (AM) and geometric mean (GM) were calculated. The latter was calculated as the mean of logarithm (EPG +1), and subtract 1 after getting the anti-logarithm.

In this analysis, individuals at baseline were defined as the exposed (absence of chemotherapy), and then at evaluation as the unexposed (with chemotherapy). Risk variables such as age and sex were set as the *a priori* confounding variables, and were used as weighting variables in the analysis.

Prevalence ratio: defined as the ratio of the proportion of individuals with the outcome (schistosome infection and/or morbidity indicators) at baseline, to the proportion of individuals with the outcome at evaluation. Standardized prevalence ratios (PRs) is defined as a weighted average of stratum-specific values that weights the stratum-specific prevalence ratios according to the product of the weight from the standard and the proportion among the unexposed. The 95% confidence intervals were derived from an appropriate variance formula (Rothman, 1986).

Standardized attributable fraction of the exposed (AFes): defined as the proportion of individuals with the outcome that were attributable to the exposure according to the product of the weight from the standard. In this study, this is the proportion of individuals with the outcome (infection and/or morbidity) at baseline that were attributable to the exposure (absence of chemotherapy) according to the product of the weight from the standard. In another words, AFes are the proportions of individuals with the outcome at baseline that were prevented by corresponding chemotherapy scheme weighted by the standard. The 95% confidence interval (CI) of AFes was estimated from the corresponding confidence limits of PRs.

Prevented number (A^0): defined as the number of cases prevented through the corresponding chemotherapy schemes. It is calculated from AFes with the expected number of cases at baseline using the standardized prevalence.

Cost-effectiveness analysis: Comparisons were made based on an overall evaluation of the three chemotherapy schemes in preventing schistosome infection and morbidity. Weighted rankings were allocated to the four measurements, that is cost per infected case prevented, cost per 1% reduction of EPG, cost per case of liver abnormality prevented, and cost per case of spleen abnormality prevented. These variables were chosen for the final assessments since they were both representative and objective measures of the overall impact of the interventions. In order to calculate the summary cost-effectiveness measure, for each variable, scores from 1 to 3 were given from the highest to the lowest unit cost. Weights of between 1 and 3 were given to each outcome indicator, with a weight of 1 to the measurement with lowest importance to a weight of 3 to the one with highest importance. In view of the objective of the global strategy for the current schistosomiasis control program, morbidity indicators were given higher weights, while infection indicators were given lower weights. In our study, liver abnormality was given a weighting of 3, spleen abnormality and infection case prevented a weighting of 2, and the outcome '1% reduction of EPG' a weighting of 1. Finally, the intervention group with highest weighted average rank was considered the most cost-effective strategy.

Sensitivity analysis: Sensitivity analysis was performed to analyze the impact of a change in key factors on the cost and effectiveness and therefore on the overall conclusions of the economic evaluations. The changes of prices of praziquantel and personnel were considered.

RESULTS

Study population

Among the total of 2,615 subjects, there were 1,451 and 1,164 males and females, accounting for 55.5% and 44.5% of the total, respectively. Males outnumbered females in all three groups, although there was no significant difference in the distribution of males and females among the three chemotherapy groups. The mean age was 27.13, 28.49 and 36.25 of subjects in Groups A, B and C, respectively. Subjects of group C were older than that of the other two groups (F=96.30, df=2, p=0.000). As indicated in earlier section, an additional 100 school aged children were included in Groups A and B, intended to increase the number of young age group subjects which were thought to be the high risk group, but later on this proved not true. The age of the subjects was then categorized into four groups, 3-14, 15-24, 25-44 and 45-65 according to the characteristics of the corresponding group and their relationship to schistosome infection. The 3-14 age group is essentially the group of primary and middle school students who are active in recreational water contact activities like swimming and playing in the water in summer. The 15-24 age group are the youth who are active in both recreational and production water contact activities. The 25-44 age group are engaged predominantly in production like farming and fishing. The 45-65 age group is the elder villagers who are less engaged in the water contact activities like farming and fishing. Only two occupations were identified–farmers and students. Though there were few pre-school children, they were included into student group. There were more farmers and few students in Group C than the other two (Table 1).

Impact on infection and morbidity

Number treated and coverage: Coverage of chemotherapy was over the required 80% except in the year 1999 for Group A (78%). In Group C, the number of subjects receiving Kato-Katz stool examination in the second year dropped considerably compared with that in the baseline survey. A proportion of the subjects (590/738, 20.1%) of the subjects failed to receive the stool examination in the case identification of the second year (Table 2).

Impacts on infection and morbidity: After chemotherapy, both the prevalence and intensity of infection (EPG) decreased significantly

Table 1
Characteristics of subjects of the three chemotherapy groups in Hunan, China.

	Clue group		Mass group		Screen group		Total	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	499	55.14	505	56.11	447	55.19	1,451	55.49
Female	406	44.86	395	43.89	363	44.81	1,164	44.51
Age group (year)								
3-14	266	29.39	276	30.67	96	11.85	638	24.40
15-24	106	11.71	87	9.67	68	8.40	261	9.98
25-44	428	47.29	378	42.00	375	46.30	1,181	45.16
45-65	105	11.60	159	17.67	271	33.46	535	20.36
Occupation								
Farmer	597	65.97	599	66.56	717	88.52	1,913	73.15
Student	308	34.03	301	33.44	93	11.48	702	26.85

Table 2
Number surveyed, treated and coverage of chemotherapy of the three chemotherapy groups in Hunan Province, China.

Group	Year	No. subjects	No. surveyed[a]	No. targets[b]	No. treated	Coverage (%)
Clue	Year 1	900	855	677	566	83.6
	Year 2	900	836	764	596	78.0
Mass	Year 1	900	-	900	881	97.9
	Year 2	900	-	900	846	94.0
Screen	Year 1	738	590	70	68	97.1
	Year 2	646	449	51	48	94.1

[a]Inquiry to contact of infested water and/or symptoms for clue group; Kato - Katz stool examination for screen group; no survey for the mass group.
[b]Those with history of contact of infected water and/or with related symptoms in clue group; Kato-Katz egg positives in screen group; all the subjects in mass group.

comparing values at baseline with those at evaluation. The crude prevalence of all the three groups decreased significantly at evaluation (χ^2_A =28.87, df=1, p=0.000; χ^2_B =37.31, df=1, p=0.000; χ^2_C=19.67, df=1, p=0.000). Similarly, the standardized prevalence of the three groups were all significantly reduced at evaluation as compared with that at baseline (χ^2_A=30.96, df=1, p=0.000; χ^2_B = 37.25, df=1, p=0.000; χ^2_C=30.41, df=1, p=0.000). The intensity of infections of the three groups also shown significant reductions when comparing the EPG(AM) at baseline with that at evaluation of the corresponding group (F_A=57.73, df=1, p=0.000; F_B=60.53, df=1, p=0.000; F_C=4.52, df=1, p=0.034) (Table 3).

Crude prevalence ratios (PR) and standardized prevalence ratios (PRs) of schistosome infection were significantly greater than 1, indicating a statistically significant reduction of schistosome infection at evaluation for all three chemotherapy groups. The PRs for schsitosome infection of the screen group were the greatest at 3.64, followed by 2.32 for the mass treatment group and 2.04 for the clue treatment group. However, variations were

Table 3
Prevalence and intensity (EPG) of *S. japonicum* infection at baseline and evaluation of the three chemotherapy groups in Hunan, China.

Group	Baseline					Evaluation				
	No.	Crude prev %	Stand prev %	EPG (AM±SD)	EPG (GM)	No.	Crude prev %	Stand prev %	EPG (AM±SD)	EPG (GM)
Clue	856	17.52	19.1	7.71±19.12	0.90	839	8.70	9.6	2.22±8.60	0.31
Mass	835	16.53	17.4	6.47±17.03	0.79	838	6.92	7.5	1.56±6.60	0.23
Screen	590	11.86	13.7	7.40±56.62	0.47	457	4.16	3.8	1.68±11.29	0.15
Total	2,281	15.69	-	7.18±32.74	0.74	2,134	7.03	-	1.84±8.57	0.24

Stand prev = standardized prevalence; EPG (AM±SD) = egg per gram feces (arithmetic mean±standard deviation); EPG (GM) = egg per gram feces (geometric mean).

observed regarding the morbidity measurements. PR for abdominal pain and diarrhea were significantly greater than 1 (reduction in prevalence) in the clue and mass groups, but were significantly smaller than 1 (increase in prevalence) in the screen groups. For liver abnormality, the prevalence significantly decreased (PR > 1) only in the mass group. The prevalence ratio was larger than 1 in the clue group and was smaller than 1 in the screen group but neither are statistically significant. For spleen abnormality, PR and PRs are significantly larger than null 1 in all the three groups. The PRs were highest at 2.80 in the screen group, followed by 1.84 in the mass group and 1.37 in the clue group.

While the PRs are different from that of the crude PR, most were only negligibly different. However, there were some indicators where standardization had a big effect in the prevalence ratios. In the screen group for example, PR of schistosome infection was 2.85, and it is 3.64 after standardization. PR of liver abnormality was 0.87, and it turned into 0.91 after standardization. PR of spleen normality was 2.46, and it turned into 2.80 after standardization. These discordances of PR and PRs indicate the confounding effect, principally the effect of difference of the age in the three groups (Fig 2).

As illustrated by standardized attributable fractions of the exposed (AFes), at least 50% of schistosome infections by means of chemotherapy in the three groups. The magnitude of AFes is 0.73 for the screen group, which is the biggest, followed by 0.57 for the mass group and 0.51 for the screen group. Corresponding to the variations of PRs, there were considerable variations of AFes for morbidity indicators. Reported diarrhea and abdominal pain were significantly attributable to the exposure (absence of treatment) in the clue and mass groups, but the results were to the contrary in the screen group. In the clue group, only 9% of the baseline liver abnormality cases could be prevented by chemotherapy, but this was not statistically significant. Chemotherapy could not demonstrate significant prevention to liver abnormality in the clue and screen groups, but it did in the mass group. On the other hand, chemotherapy prevented significant proportion of spleen abnormality in the mass and screen groups, but not in the clue group (Fig 3).

Number of cases prevented attributable to chemotherapy schemes: The estimated number of schistosome infection cases prevented were 86, 83 and 59 for the clue, mass and screen groups, respectively. The number of morbidity cases prevented by corresponding chemotherapy schemes varied as shown in Table 4.

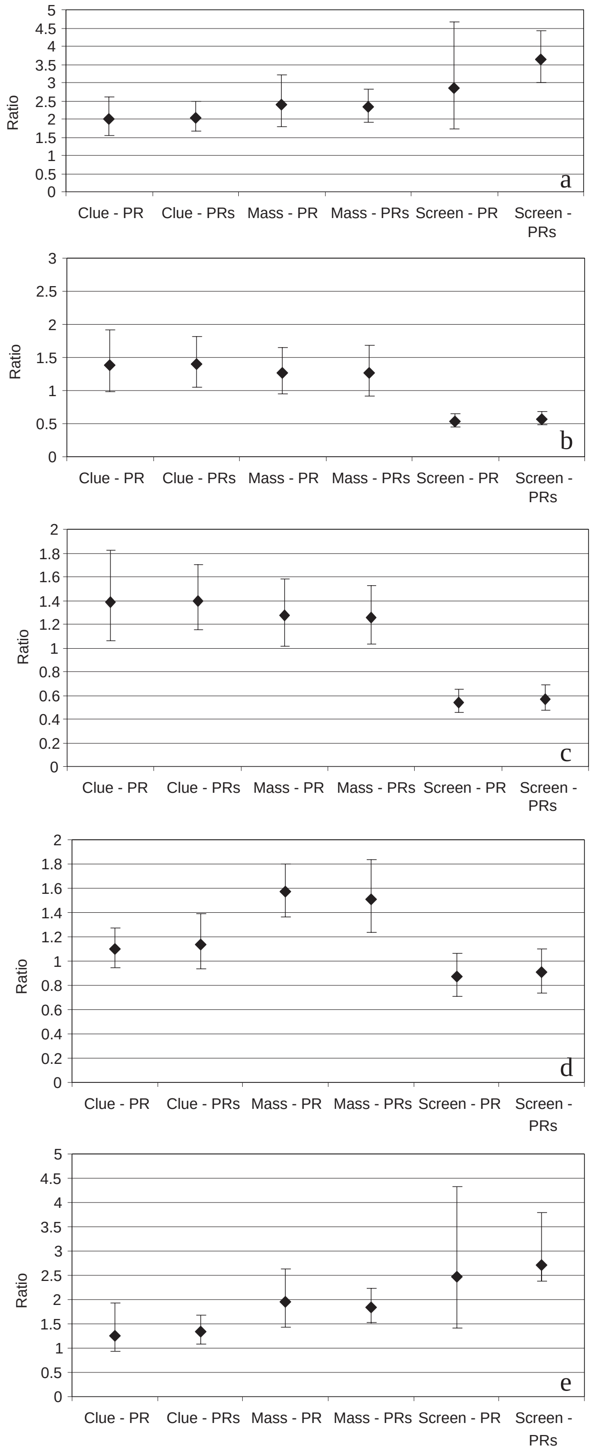

Fig 2–Crude (PR) and standardized prevalence ratios (PRs) of variables of *S. japonicum* infection in Hunan, China. a) S.j. infection; b) Abdominal pain; c) Diarrhea; d) Liver abnormality; e) Spleen abnormality.

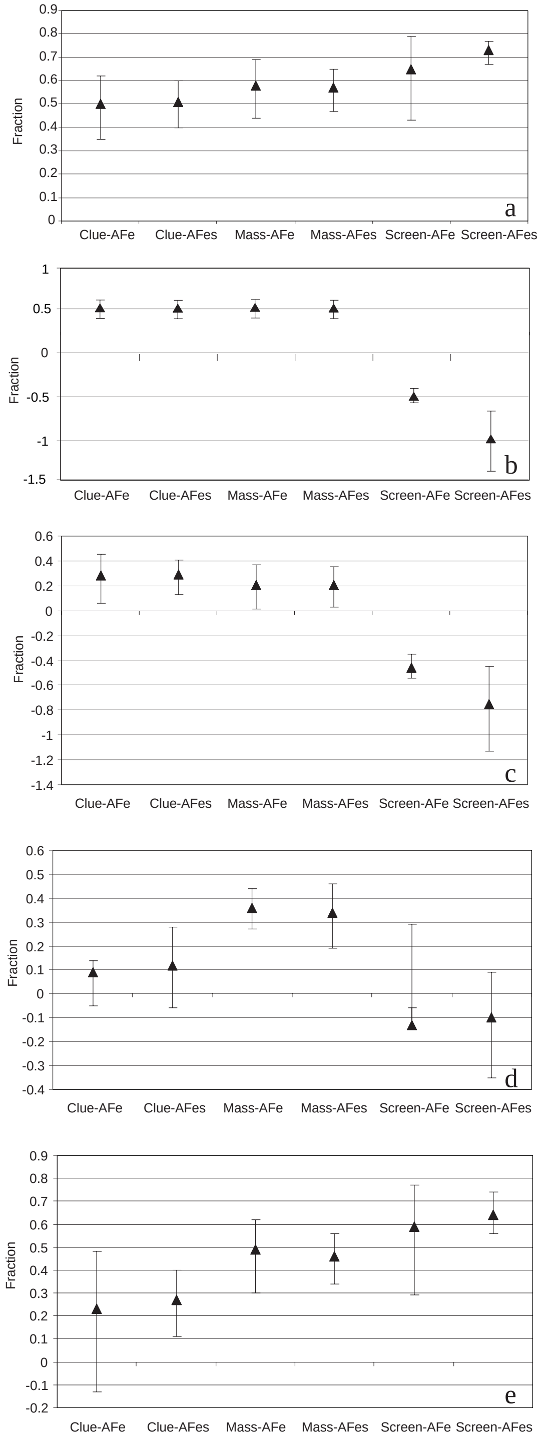

Fig 3–Crude (AFe) and standardized attributable fraction (AFes) of variables of *S. japonicum* infection in Hunan, China. a) S.j. infection; b) Abdominal pain; c) Diarrhea; d) Liver abnormality; e) Spleen abnormality.

Table 4
Number of schistosome infection and morbidity cases prevented by corresponding chemotherapy schemes in Hunan, China.

Group	Measurements	Pfes	No. expected cases[b]	No. cases prevented
Clue	Schistosome infection	0.51	169	86
	Abdominal pain	0.49	195	95
	Diarrhea	0.29	124	36
	Liver abnormality	0.12[a]	341	41[a]
	Spleen abnormality	0.27	76	20
Mass	Schistosome infection	0.57	145	83
	Abdominal pain	0.48	280	134
	Diarrhea	0.21	154	32
	Liver abnormality	0.34	394	134
	Spleen abnormality	0.46	132	61
Screen	Schistosome infection	0.73	81	59
	Abdominal pain	-0.96	125	-
	Diarrhea	-0.75	130	-
	Liver abnormality	-0.10[a]	123	-
	Spleen abnormality	0.64	39	25

[a]Not statistically significant at significance level of 0.05.
[b]It was derived from the single standard number at baseline multiplying the standardized prevalence.

Cost analysis

Considering that there was inflation (official figure 1-2% during the years 1998-2000) in China during the study period, the intervention costs in later years of the study were not discounted to the base year (therefore assumed discount rate of 0%). The total cost of the three groups were RMB 12,053.3 yuan, 13,379.0 yuan and 11,210.6 yuan, for Groups A, B and C, respectively. Table 5 presents a summary of the cost results.

In the three groups, personnel costs accounted for the largest proportion of expenditure, followed by consumables. In Groups A and B, the third largest expenditure was on capital items, and in Group C the third largest expenditure was for vehicle cost, followed by other capital costs. Diagnosing and treatment accounted for the largest shares of costs in the three groups. In Group A, treatment accounted for the largest share of cost, followed by diagnosis. In Group B, treatment was the activity that accounted for the majority of the cost. However, in Group C diagnosis accounted for the largest share, followed by treatment.

Cost-effectiveness analysis

The cost-effectiveness results are presented in Table 6. The costs per schistosome infection case prevented during the two-year period were RMB yuan 140.2, 161.2 and 190.0 for the clue, mass and screen groups, respectively. The cost of preventing schistosome infections was lowest in clue group, followed by the mass group, and the highest in the screen group. The unit cost of 1% reduction of EPG of schistosome infection was 145.0 yuan for screen group, 176 yuan for the mass group, and 169.3 yuan for the clue group. The cost per case of liver abnormality prevented was highest in the clue and screen groups, as there was not a significant number of cases prevented, and lowest in the mass group. For unit costs of preventing a case of spleen abnormality, it was highest in clue group, followed by the screen group, and was lowest in mass group. Through comprehensive assessment, the mass group has the highest weighted ranking and thus was concluded to be the most cost-effective schemes among the three. Screen chemotherapy, on the contrary, was the least cost-effective option (Table 6).

Table 5
Costs of the three chemotherapy groups by year, categories of expenditures and activities in Hunan, China.

		Clue Group	Mass Group	Screen Group
Total		12,053.3	13,379.0	11,210.6
By year				
	Year 1	5,982.1	6,743.9	6,217.9
	Year 2	6,071.2	6,635.1	4,992.7
By category of expenditure				
	Personnel	7,860.0	7,860.0	7,320.0
	Consumables	3,937.3	5,348.3	1,958.8
	Vehicle	0	0	1,650.0
	Capital	256.0	170.7	281.8
By activities				
	Supervision	660.0	660.0	660.0
	Mobilization	480.0	480.0	180.0
	Training	480.0	480.0	180.0
	Diagnosis	2,545.5	0.0	6,840.0
	Treatment	7,887.8	11,759.0	3,413.0

Table 6
Unit cost of prevented infection and morbidity case and comprehensive assessment of three chemotherapy schemes in Hunan, China.

Group	Preventing 1 case of infection (Weight 2)			1% reduction of EPG (Weight 1)			Preventing 1 case with liver abnormality (Weight 3)			Preventing 1 case with spleen abnormality (Weight 2)			Weighted average rank
	Cost	Rank	WR	Cost	Rank	WR	Cost	Rank	WR	Cost	Rank	WR	
Clue	140.2	3	6	169.3	2	2	-	1.5	4.5	602.7	1	2	3.63
Mass	161.2	2	4	176.3	1	1	99.8	3	9	219.3	3	6	5.00
Screen	190.0	1	2	145.0	3	3	-	1.5	4.5	448.4	2	4	3.38

WR = rank multiplied by weight.

Sensitivity analysiss

Total costs were found to be sensitive to changes in personnel cost in all the three groups, with the total costs of the clue and screen groups being the most sensitive, assuming all other costs to be constant.

In the future, it is expected that the cost of the essential drug praziquantel would decrease, since the patent of the drug has expired (Doenhoff *et al*, 2000). The mass group would be most sensitive to this price reduction, and naturally there would be a sharp decrease in the total cost if the cost of PZQ was deceased by half. Costs of the clue group would also decrease but the proportional reduction in cost would be less than that of the mass group. The cost of the screen group would be the least sensitive to the changes of the cost of PZQ, and there would be almost no significant changes even if the cost of PZQ drops by 50%.

In our study, the targets determined by clue chemotherapy scheme were as high as 85.21%

(1,441/1,691) of the total subjects surveyed. Undoubtedly this was too high due to the unusually heavy floods that year. However, if the number of targets of clue chemotherapy were only half of the current number as would have happened in average years, we would expect a 12.20% (2,940*0.5/12,053) reduction of the total cost due to reduced drug cost in clue group, assuming all other costs and costs of other groups constant. This scenario would have made clue chemotherapy scheme more favorable to the mass chemotherapy scheme.

Obviously, Kato-Katz examination of one stool sample with three slides is not sensitive especially in endemic areas where level of infection is not very high. One would expect considerable number of true positive cases missing in the examination. We could have increased the number of stool samples to be examined in order to increase the detection of true infections. If we increased the number of specimens for stool examination by one, the total cost of screen group would be increase by about 61% (6,840/11,210). However, this significantly marginal increase of cost could yield about 3-5% increase of the total number detected. Under this scenario, the cost-effectiveness of the screen chemotherapy scheme could be worse than the current situation, which was already the least cost effective one among the three schemes.

There are two possible scenarios which would possibly affect the total cost of the three groups by different prevalence of infection, one with higher prevalence in the endemic villages while the other with lower prevalence. These two scenarios however would have significantly less effect, or even no effect at all, on the total costs of the mass and clue chemotherapy schemes, since almost all the residents would undergo treatment under the above two schemes, whether the prevalence was higher or lower. However, it would be reasonable to expect that if the prevalence is higher than the current situation, the total cost of the screen group would not significantly increase and the cost-effectiveness would also improve. This is because more cases with both infection and morbidity would be detected with the same amount of inputs. Though it would be difficult to estimate the magnitude of the changes in cost effectiveness in the three groups, it can hardly be expected to change the current conclusion even if the prevalence was twice the current level.

DISCUSSION

Schistosomiasis is a disease endemic in the tropical and subtropical world, affecting mostly the poorer and marginalized population of the endemic developing countries. The tools and measures to fight against this deadly parasite are readily available, but the resources are not always. It is therefore a key issue for policy makers and health care planners that the benefits of the available resources are maximized. In China, the major endemic areas for *S. japonicum* are in the marshland and the lake regions. The areas of habitats for *Oncomelania* snails are extensive, and are increasing year by year due to the silt deposition. Elimination of snails in these areas is obviously impossible at the current stage. On the other hand, praziquantel is an effective and highly safe schistosomacidal agent, widely available and is getting cheaper due to the expiration of the patent. Moreover, in our recent field evaluation study the drug has been shown to be highly effective against *S. japonicum* in a region where extensive mass chemotherapy has been applied for more than fourteen years. There was no sign of intolerance or resistance as is more likely to be the case in Africa (Yu *et al*, 2001). We thus expect that chemotherapy with praziquantel could serve as one of the principal control strategies for the current control program in the foreseeable future.

In a context where the prevalence of *S. japonicum* was high but the intensity of infection was low, the most cost-effective way of delivering praziquantel chemotherapy against *S. japonicum* infection was mass chemotherapy, that is, treatment of every possible one in the endemic community. This seems not in line with the results reported by Lin *et al* (2000) in Jiangxi

Province. In their study, mass chemotherapy was less cost effective than selective chemotherapy screened by Kato's examination or with McAb-Dot-ELISA in terms of cost of reduction of 1% of prevalence of infection per 100 persons. This result, however, was not surprising, since the measurements of outcomes were not the same as in this study. In our opinion, a reduction of prevalence alone could not fully demonstrate the effectiveness of chemotherapy.

The so-called "clue" chemotherapy was demonstrated to have the lowest cost in preventing infections and morbidity in the study areas. Theoretically, this scheme was designed to refine the targets of mass chemotherapy by screening the subjects through a simple inquiry about the history of water contact as well as symptoms relevant to schistosome infection. Such a technique aims to reduce the cost and work load involved in the delivery of mass treatment, and also the wastage of drugs. This scheme, however, can in practice become a mass treatment. For example, the Dongting Lake region in 1998 was hit by the worst flooding in more than 40 years in the region, and in that year a significant portion of the residents participated in controlling the flood. The proportion of residents with water contact was extremely high and thus the "clue" chemotherapy turned into a *de facto* mass chemotherapy. The consequence was that the objectives and advantages of this scheme could not be fulfilled. However, we still believe that this strategy has the advantage of reducing the costs of mass chemotherapy through better targeting of subjects of chemotherapy, especially when the compliance of mass chemotherapy had been declining after years of practicing mass chemotherapy.

The conclusions of a similar study in Jiangxi (Jiang, *et al*, 1999) were not in contradiction with our current study, although there were one or two minor differences. First, clue chemotherapy was found to be more cost-effective compared to mass chemotherapy in reducing infection rates. Second, only 35.21% of the subjects were identified as targets of treatment using "clue" therapy in their study, compared with 85.22% in our study. Third, cost estimation was not explained in their study, and the measure of effectiveness was not fully inclusive and therefore comparable to our own measure. On the other hand, from our sensitivity analysis, it was shown that if clue therapy identified only half the number of subjects for treatment, total costs of this strategy would be reduced by 12% from the reduction of drug cost alone. This result might have changed our current conclusion and make "clue" chemotherapy more favorable to mass chemotherapy in terms of cost-effectiveness.

Screen chemotherapy was shown to be the least cost effective scheme and thus the least favored among the three strategies. The result was not surprising considering the intensive labor input required and the low sensitivity of Kato-Katz technique in areas with low-level intensity of infections. Case identification for schistosomiasis in the field has proven to be difficult. On the one hand, after years of mass chemotherapy, the intensity of infection has decreased substantially. It is well known that Kato-Katz thick smear technique has low sensitivity when the intensity of infection is low, though it is relatively easy and convenient to use. Other stool examination techniques such as stool egg sedimentation and concentration are more labor consuming and thus difficult for field use. On the other hand, serological tests with higher sensitivity such as IHA and ELISA could hardly be utilized in these areas since they cannot differentiate current from past infections. Re-infections are quite frequent in these areas, as the sources of infection have not been removed. Our experience in the field also demonstrated that villagers were not fond of stool examination, and are likely to be especially against this strategy if it was carried out every year. From the economic point of view, it seems that case identification by stool examination is not a favorable choice, and efforts could well be concentrated on mass or clue chemotherapy.

The current study demonstrated that chemotherapy with praziquantel resulted in a significant and concrete impact on *S. japonicum* infection in the residents. This result was in line with a number of other recent studies carried out throughout the country (Li *et al*, 1997; Liang *et al*, 2001; Yu *et al*, 2001). In all three areas, there were significant reductions of both prevalence and intensity of schistosome infection after the two-year chemotherapy campaign in the villages. However, the impact on morbidity as indicated by the cases with diarrhea and abdominal pain, and abnormality of liver and spleen, prevented by the intervention were not straightforward but with considerable variations. For cases with symptoms and abdominal pain, there was a significant reductions in the number of cases in the villages where mass and clue chemotherapy schemes were applied. However, in villages with screen chemotherapy, there was an increase in the number of cases compared with the period before chemotherapy. One of the obvious reasons was that there had been an epidemic of gastro-enteritis among the villagers in this clue group a month prior to the survey. A substantial proportion of the residents reported occurrence of abdominal pain and diarrhea during that period of time. This again demonstratesd the unreliability and of these variables as indicators for morbidity in assessing schistosome infection in the endemic community, as Hagen (1996) pointed out.

Generally speaking, liver and spleen abnormality directly observed by ultrasonography are more direct and objective for evaluating the impact on morbidity in liver and spleen by chemotherapy schemes (Butterworth *et al*, 1996; Gryseels, 1996; Vennervald *et al*, 1998), and our study has confirmed these views. As observed, there was high prevalence of liver abnormality related to schistosome infection in all the study communities, demonstrating significant pathological changes among the residents in the endemic areas resulting from continuous and repeated exposures to schistosome infection, as Olds *et al* (1996) also observed. These findings also remind us of the necessity for sustainable and long term interventions against schistosome in the area.

It should be realized that this is only a two-year intervention and evaluation study. The period between the last treatment and evaluation was only six months, which may not demonstrate the full impacts of the different schemes. Therefore, it could be concluded from our current study, as well as other studies, that chemotherapy with praziquantel treatment had a far more significant and straightforward impact on *S. japonicum* infection than on morbidity in this kind of endemic areas (Olds *et al*, 1996; Li *et al*, 1997; Ross *et al*, 1998; Lin *et al*, 2000).

The core of the current analysis was using the prevalence ratio as an estimator for risk. This study was a repeated cross-sectional study of the same population cohorts, though a small portion of the subjects examined at baseline were different from that at evaluation. It is well known that prevalence ratios and related measures are derived from the methods developed specifically for cohort studies. They can be applied to cross-sectional data to estimate the "risk" but with certain pre-conditions and assumptions. Firstly, quite a number of field studies have demonstrated the "causal" relationship between schistosome infection and the occurrence of related morbidity, such as liver and spleen problems in the endemic areas (Booth *et al*, 1996; Li *et al*, 1997; Ross *et al*, 1997). We could reasonably assume in this study that schistosome infection is the *a priori* "risk" factor, and chemotherapy as an intervention could remove the above factor, and thus preventing infection and morbidity relating to the infection. The second, the basic assumptions for using PR to estimate the relative risk, is that there is a steady state status: the mean duration of the disease is the same for the exposed and unexposed populations, and other diseases do not affect exposure status. All these conditions are assumed to have met in this study. It is therefore reasonable and valid to use PR as estimator of risk in this study.

Though the methodology used is valid in estimating the outcome of interventions since there is an epidemiological basis, there are possible limitations in estimating the number of cases prevented when the baseline prevalence of the groups are different. In our study for example, the standardized prevented faction of schistosome infection in the screen group is higher than the other two groups. However, it turned out that the number of cases prevented to be less than the other groups mainly because the baseline prevalence was lower than the other two groups. Therefore, in interpreting these results it should be taken into account that the comparison groups are assumed to have similar prevalence levels when this method is applied.

From our study, it is concluded that chemotherapy with praziquantel could significantly reduce the prevalence and intensity of schistosome infection in the hyperendemic areas of schistosomiasis japonica in Hunan Province of China, be it mass treatment, selective treatment to the residents with contact with infested water in the past year and/or symptoms like abdominal pain and diarrhea of the previous two weeks, or treatment to the infected individuals after stool examination. However, the impacts on the morbidity related to schistosome infection, *ie*, abdominal pain, diarrhea and ultrasonographic liver and spleen abnormalities, were not as straightforward as the treatment of infection itself. Though all three chemotherapy schemes reduced liver and spleen abnormalities to different extents, as demonstrated by ultrasound examination, the reduction of symptoms varied among groups, which also indicate that the use of those symptoms as morbidity indicators is unreliable. Our cost-effectiveness analysis showed that, in the given study context, the mass chemotherapy scheme was the most cost- effective in term of infections and morbidity prevented and percentage reduction of intensity of infection. The second most cost-effective strategy was the clue chemotherapy scheme, and the least cost-effective one was the screen chemotherapy scheme. It was also demonstrated that this conclusion could be further strengthened if the price of praziquantel is reduced, which is likely to be the case in the near future.

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