Schistosomiasis Japonica in the Philippines: The Long-Term Impact of Population-Based Chemotherapy on Infection, Transmission, and Morbidity


The long-term impact of annual case-finding and chemotherapy with praziquantel on schistosomiasis japonica was examined in an 8-year longitudinal study in the Philippines. The prevalence, incidence, and intensity of infection and schistosome-induced hepatomegaly significantly decreased within 3–4 years of treatment and then stabilized despite continual population-based chemotherapy. Hepatomegaly rapidly developed in acutely infected persons, with 82% of subjects developing hepatic enlargement within 2 years of reinfection. These data suggest that abrupt discontinuation of current control measures in the Philippines may result in a rapid rebound in morbidity. Age-dependent acquired resistance to reinfection also developed in subjects chronically exposed to schistosomiasis japonica, suggesting that a vaccine may represent an alternative approach for control of this parasitic infection.

Schistosomiasis japonica is a major health problem in the Philippines and China [1, 2]. Infection with *Schistosoma japonicum* leads to a significant delay in growth and development in children and to hepatosplenomegaly [3–5]. With time, schistosome-induced hepatic fibrosis develops, which leads to portal hypertension and esophageal varices [5]. Mortality due to schistosomiasis japonica has been estimated to be 1.8% per year before the use of praziquantel [5]. The life cycle of *S. japonicum* occurs between the human host and a small amphibious snail, *Oncomelania* species [5]. In contrast to the transmission of other schistosome species, the transmission of *S. japonicum* in endemic areas is contributed significantly by animal reservoirs, such as cattle and water buffaloes [5].

In the Philippines, 10 million people live in areas endemic for schistosomiasis japonica, and >500,000 are actively infected [3, 6]. The major foci for transmission are located on the islands of Leyte, Samar, and Mindanao. Rice farming is the predominant occupation in these endemic areas, which allows for maximal contact between humans, animal reservoirs, and the freshwater snail intermediate host.

Praziquantel is currently the drug of choice for treatment of *S. japonicum* infection. This drug achieves parasitologic cure rates often >90%, with minimal side effects [7]. Praziquantel is expensive but it is the only acceptable and effective drug for treatment of this species of schistosome [8]. Since praziquantel is safe and can be orally administered, it has become the basis of community-based chemotherapy programs for control of schistosomiasis japonica in the Philippines and China.

In 1981, a community-based treatment and morbidity study in three villages in rural Leyte was initiated [9]. Villages were screened annually for *S. japonicum* infection, and infected persons were treated with praziquantel. Because of the success of this approach, the Schistosomiasis Control Program, organized by the Department of Health in the Philippines, began to survey and treat all inhabitants on the islands of Leyte and Samar using this strategy. This ambitious project managed to examine and treat almost 400,000 cases by 1984 [10].

In 1985, external funds were withdrawn and the scope of the program was severely reduced. Consequently, a subproject of this study was initiated in 1986 to determine the impact of increasing the interval between community surveys for villages for which the prevalence of infection was <10%. Since these areas represented 60%–80% of the population at risk for schistosomiasis in the Philippines, this strategy would have allowed a more cost-effective allocation of limited domestic funds [10].

Here we describe the impact of this long-term community-based program on infection and morbidity induced by schistosomiasis japonica in three villages on Leyte [9]. In addition, since this study followed >5000 subjects over 8 years, we had the opportunity to examine these data for evidence of acquired...
Methods

Study population. The study population consisted of all persons ≥1 year old in three rural villages in northeastern Leyte [9]. Chemotherapy-based schistosomiasis control was nonexistent before the initiation of this study. A census was done yearly to assess population movement and growth. Transmission of schistosomiasis occurs throughout the year, and malaria is not endemic. Rainfall is continuous throughout the year, with no distinct dry seasons. Rice farming is the primary occupational activity.

Study design. The study design was longitudinal over 8 consecutive years (1981–1989). Medical histories, quantitative stool egg counts, and abdominal physical examinations were done yearly. Stool samples from all subjects were examined at baseline and every 3 months during the first year of the study. Thereafter, annual physical and stool examinations were done. Basic demographic information, including date of birth, age, and sex, were obtained from each subject on entry into the study or from parents of subjects <16 years of age. All infected subjects were treated with praziquantel (Bayer, Leverkusen, Germany), 50 mg/kg orally in two divided doses 4 h apart [10]. Pregnant women were exempt from treatment until after delivery. In years 6 and 7, villages A and B were screened, but treatment was intentionally deferred so that the optimal interval between screening and treatment could be determined for villages with initial low prevalences of infection.

Clinical and parasitologic examinations. Annual parasitologic examinations were done on a single stool sample obtained from each subject. Single stool samples were examined since, despite the potential of missing infected persons, this project was a model to evaluate the effectiveness of the national control program in the Philippines. From each sample, duplicate 50-mg Kato-Katz thick smears were prepared [11]. The presence of S. japonicum eggs was confirmed independently by 2 microscopists. An independent expert microscopist randomly examined 10% of all slides to assess the quality of field diagnosis, and >99% correlation was observed for all years.

Liver size was determined by palpation and recorded as the distance in centimeters below the costal margin in the right midclavicular line and below the xiphoid process in the midsternal line [9]. Significant hepatomegaly was defined as a liver edge >2 cm below the costal margin in the midclavicular line and >3 cm in the midsternal line. Subjects were also examined for the presence of splenomegaly (unpublished data). Ten percent of all subjects were examined blindly by 3 different examiners during each field survey to assess interobserver variability of physical examination results. More than 94% correlation was found on all occasions. Conflicting results were invariably due to the inability to palpate accurately the liver in the midsternal line because of the muscular rectus muscle in young men and obese subjects.

Data analysis. Compliance with physical examination, stool examination, and chemotherapy and the average growth of the community was determined annually. Each year, the prevalence of infection was calculated among all subjects examined. The incidence of infection was also estimated each year among subjects at risk for infection. This estimate was calculated using all subjects who were negative for S. japonicum eggs on Kato-Katz smears. In addition, all infected subjects who were treated with praziquantel were considered at risk for infection and included in the calculation, since the treatment efficacy with praziquantel was found to be >98%. Some subjects had 1 or more years of missing data because of noncompliance with annual stool examinations. These subjects were assigned an equal probability of becoming infected within each of the yearly intervals between their consecutive examinations. The χ² test was used to compare proportions. Geometric mean egg counts of infected subjects between each year of the study were compared by Student’s t test.

The rate of development of hepatomegaly due to schistosomiasis was determined using a failure-time analysis for subjects who initially did not have hepatomegaly on physical examination but subsequently became infected with S. japonicum [12, 13]. The probability of developing hepatomegaly over time was estimated as 1 minus the Kaplan-Meier estimate of survival without developing significant hepatomegaly. All infected subjects contributed to this estimate. Time points beyond 1 year were generated from subjects for whom treatment was intentionally deferred (villages A and B during years 6 and 7) and from several hundred other subjects who were infected with S. japonicum but were not treated at the time of diagnosis since they did not return for therapy. Although not randomly selected, this cohort was comparable to the study population with regard to age, sex, and intensity of infection and thus allowed assessment of the probability of developing hepatomegaly over time.

Failure-time analysis was also used to examine the time interval for reversal of hepatomegaly in subjects infected with S. japonicum who had hepatomegaly at the time of treatment with praziquantel. Subjects who became reinfeeted before hepatomegaly resolved were excluded from this analysis. Furthermore, for subjects who had multiple infections that were treated and were associated with resolution of hepatomegaly, only their initial infection and treatment was used for analysis.

The time to infection was defined as the interval between the entry of a subject into the study and development of infection with S. japonicum. Subjects who entered the study were screened for the presence of S. japonicum infection and, if infected, were treated with praziquantel. Thus, after the initial screening and treatment in year 1, all subjects were considered uninfected. Time to infection for each case was calculated by subtracting the date of entry into the study from the date of infection, which was estimated as midway between the last uninfected examination and the first positive examination as determined by the presence of S. japonicum eggs in the stool. For each subject, the first case of infection or reinfection after entry into the study was used for that subject in order to avoid overrepresentation of subjects with multiple infections with S. japonicum over time. A few subjects who were initially infected but inadvertently or intentionally not treated were omitted from analysis until they were subsequently shown to be treated.

The length of participation in the study was determined for those subjects who never became infected.
Time-to-infection curves were calculated for subpopulations stratified by age and by village. Analysis stratified by villages was done when the incidence of infection stabilized after intensive screening and chemotherapy. Years 1 and 2 after initiation of the study were excluded for villages A and B and years 1, 2, and 5 for village C. Year 5 was excluded for village C since the incidence of infection increased significantly after disruption of the water supply. Since two distinct periods of stable prevalence of infection were observed in village C, these were analyzed separately and designated C-1 for the first plateau phase, which included years 3 and 4, and C-2 for the second phase for years 6 and 7. Comparisons between time-to-infection curves were done using the log-rank test.

Results

Study population. A total of 5122 subjects were enrolled in the study over 8 consecutive years from November 1981 through March 1989. Village populations at the beginning of the study were as follows: 341 in Santol (village A), 1008 in Santa Rosa (village B), and 1241 in Macanip (village C). Compliance with providing stool samples for examination during the initial year of the study was 85%, 82%, and 90% in villages A, B, and C, respectively. In subsequent years, the compliance rate remained similar or increased compared with the first year of the study. For example, in 1989, compliance was 92%, 90%, and 94% in villages A, B, and C, respectively. The growth rate of the study population was estimated to be 4% per year, which included new births and immigrants as well as deaths and emigration to other areas. The average flux of villagers into and out of the study was 12% per year.

Infection with *S. japonicum*. The impact of annual screening and treatment of infected subjects with praziquantel is shown in figure 1. The prevalence of infection at the beginning of the study before treatment was 25%, 37%, and 44% for villages A, B, and C, respectively [9]. Treatment of all infected subjects over a 3-year period was associated with a steady decrease in the prevalence of *S. japonicum* infection. The prevalence of infection stabilized at 4%–6%, 7%–9%, and 11%–13% in villages A, B, and C, respectively, in years 3 and 4 (figure 1).

In village C, the prevalence of infection increased from 13% in year 4 to 24% in year 5 and stabilized at this level until the end of the study period in year 7, despite annual case finding and therapy (figure 1). This increase was associated with disruption of the piped water supply caused by a typhoon in year 5. In contrast, when treatment was deferred for 2 years during the field surveys in years 6 and 7, the prevalence of infection in villages A and B did not increase (figure 1). When analysis was restricted to the cohort of 396 subjects who participated in the survey for all 8 years of the study, the change in the prevalence of infection was not significantly different from that observed for the community.

The incidence of infection determined at the first follow-up survey 1 year later was 12%, 9%, and 22% in villages A, B, and C, respectively (figure 1). The incidence of infection then decreased over the next 2 years to 3% in village A, 5% in village B, and 8% in village C and stabilized at these levels. These changes paralleled the changes observed in the prevalence of infection for the community during this time period. Furthermore, the incidence of infection did not increase in villages A and B when treatment was deferred for 2 years in years 6 and 7. However, the incidence of infection increased in village C to 18%–21% despite yearly surveillance and treatment during the last years of the study coincident with the disruption of the piped water supply. Similar results were observed in the cohort of subjects followed for the entire study period.

![Graph](image_url)
The geometric mean of egg output of infected subjects in the study population decreased significantly ($P < .001$), from 85 eggs/g of stool in the initial year of the study before treatment to 27 eggs/g of stool by year 2. Thereafter, the mean egg count was relatively constant for the remainder of the study, ranging from 26 to 35 eggs/g of stool.

To determine the sensitivity of duplicate Kato-Katz smears on a single stool sample to detect *S. japonicum* infection, 4 daily consecutive stool samples were analyzed on 38 subjects ages 11–18 years. *S. japonicum* eggs were found in stools of 53% (20/38) in the initial stool examination, while 82% of subjects (31/38) had eggs in their stools when 4 samples were examined over time. All subjects were lightly infected, with egg counts <50/g of stool. These data suggest that duplicate Kato-Katz smears done on single stool samples missed at least 35% of infected subjects.

*S. japonicum*-associated morbidity. The prevalence of hepatomegaly defined as $\geq 3$ cm in the midsternal line or $\geq 2$ cm in the midclavicular line was 18% (135/763) in infected subjects in the first year of the study, which was significantly greater ($P < .001$) than among uninfected persons (8.3%; 104/1254) in the community. The prevalence of hepatomegaly in the community, which included both infected and uninfected persons, declined from 12% in the initial survey to 6% (86/1463) within 5 years of starting the control program. No further decrease in the prevalence of hepatomegaly was noted, despite continual annual screening and treatment.

The rate of development of hepatomegaly due to schistosomiasis japonica was examined in subjects who were initially uninfected with *S. japonicum* but who later became infected during the course of the study (figure 2A). Of subjects without hepatomegaly, 72% (422/582) had liver enlargement within 1 year of infection; within 2 years, 82% (175/213) demonstrated hepatic enlargement. Specific rates for different age groups and subjects with different intensities of infection could not be determined because of the small size of the cohort remaining untreated for 2 years. These results were seen in subjects who were intentionally not treated in villages A and B in years 6 and 7 and in subjects who were noncompliant with treatment follow-up. This rapid and striking increase in the prevalence of hepatomegaly in association with a delay in treatment was unexpected and led to discontinuation of the arm of the study that examined the optimal interval between periodic surveys for *S. japonicum* infection.

Regression of hepatomegaly following treatment of infected subjects with praziquantel was also examined (figure 2B). When subjects with hepatomegaly identified at the time of diagnosis of infection with *S. japonicum* were treated, only 51% (55/108) of this cohort had hepatomegaly 1 year later. By 4 years after treatment, hepatomegaly was found in 6.6% (7/106) of this cohort provided they remained free of infection. This residual prevalence of hepatomegaly was similar to that observed in uninfected persons at the start of this study (8.3%) [9]. No significant differences were observed in the rate of reversal of hepatomegaly when the analysis was stratified by age or sex.

Changes in the age-specific prevalence of hepatomegaly among subjects infected during year 1 and years 5–7 of the study in village C are shown in figure 3. Data in years 5–7 were aggregated in order to increase the number of infected subjects for this analysis. Results from the first examination in years 5–7 were used to avoid overrepresentation of subjects with multiple infections. Only village C is shown, since treatment was deferred in villages A and B in the last 2 years of
Figure 3. Age-specific prevalence of hepatomegaly among subjects infected with *Schistosoma japonicum* in first year of study (before use of community-based chemotherapy) and last 3 years of study (after intensive yearly screening and chemotherapy) in village C. No significant differences ($\chi^2, P < .05$) were found between year 1 and years 4–6.

The prevalence of hepatomegaly peaked at 32% among 10- to 14-year-olds and decreased in older subjects. No significant differences were noted in the age-specific prevalences of hepatomegaly of infected subjects surveyed in year 1 and the last 3 years of study. These data suggest that the prevalence of hepatic enlargement in the infected population was relatively unaffected by continuous screening and treatment. Thus, the impact of yearly treatment of infected subjects on the reduction in hepatomegaly in the community appeared to be almost entirely due to an overall decrease in the number of cases of schistosomiasis.

Evidence for acquired resistance for schistosomiasis japonica. Transmission of schistosomiasis was characterized using failure-time analysis. When the time to infection was compared between villages, it was significantly ($P < .001$) longer in villages A and B than in villages C-1 and C-2 (figure 4A). Furthermore, in village C, the time to infection was significantly ($P < .001$) longer in village C-1, before disruption of the water supply, than in village C-2, when a safe water supply was no longer available.

Time-to-infection curves for different age groups are shown in figure 4B. These age groups were selected to reflect in part the age-specific activities and exposures in this population and to allow sufficient sample sizes in each age group for analysis. These age groups included children before entry into school (0–6 years), schoolage children (7–13 years), young adults working in the fields (14–35 years), and adults (>35 years). Children <6 years old were infected more slowly than the older age groups, consistent with the lack of exposure to infected water until age 3–4 years. In contrast, children ages 7–13 were infected significantly ($P < .001$) more rapidly than were subjects >14 years or children <6 years old. When the 7- to 13-year-old age group was further analyzed with respect to sex, boys were infected significantly ($P < .001$) more rapidly than girls (data not shown).

Time to infection was also analyzed on the basis of infection status at entry into the study (figure 5). In children ages 7–13 years, no significant differences were observed between those initially uninfected and those who were infected and then treated with praziquantel. However, subjects ages 14–35 years who had a history of active infection and were treated with praziquantel became reinfected significantly ($P < .001$) more slowly than subjects who were not infected on entry into the study (figure 5). This difference was seen for both males and females. Five years after treatment, however, this difference was no longer observed (figure 5B). Since there were only a few subjects in the cohort at 5 years, the significance of this observation is unclear.

Discussion

This study demonstrated that population-based treatment with praziquantel was an effective strategy to reduce infection and morbidity due to schistosomiasis japonica in northeastern Leyte. Case finding and treatment were significantly associated with a striking decrease in the prevalence, incidence, and intensity of infection within 3 years of initiation of the survey. With continual annual screening, the prevalence and intensity of infection persisted at significantly lower levels. The reduction in the intensity of infection, as determined by a significant decrease in egg output, suggested that the worm burden in infected subjects also markedly decreased after treatment.

These data confirmed previous studies that demonstrated that the prevalence and incidence of schistosomiasis decreased over time after implementation of successful population-based chemotherapy programs, presumably through a drop in the rate of
the life cycle of *S. japonicum* in areas in which it is endemic [17]. These reservoirs consist of domestic animals, such as water buffalo, dogs, and pigs, and wild animals [17, 18]. Treatment of these reservoirs is expensive, and the difficulty in identifying infected animals has precluded inclusion of this strategy into the national control program in the Philippines. Other approaches, such as the use of public works projects and molluscicides, are quite expensive and have been ineffective in interrupting transmission in the Philippines [3]. Thus, for the foreseeable future, population-based chemotherapy will remain the basic control strategy for schistosomiasis japonica in the Philippines.

Another explanation for the limited impact on schistosomiasis japonica despite intensive chemotherapy is that Kato-Katz smears missed significant numbers of infected persons. In this study, duplicate Kato-Katz smears of single stool samples were used to detect *S. japonicum* infection, since multiple stool examinations for each subject over this 8-year period would have been impractical and expensive. Furthermore, since the overall reinfection [14–16]. It is assumed that this was due to a reduction in the number of infected humans contributing eggs into the environment. The failure of villages A and B to demonstrate a significant increase in the incidence of infection when treatment was deferred for 2 years suggested that this reduction is relatively durable in villages for which the rate of new infection was relatively low.

Despite very high compliance by the local population and high cure rates with praziquantel, transmission of schistosomiasis japonica was clearly not eradicated. This is not surprising since, in contrast to the case with *Schistosoma mansoni* and *Schistosoma haematobium*, nonhuman reservoirs can maintain

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**Figure 4.** Time to infection with *Schistosoma japonicum* as stratified by village (A) and age (B). Time to infection of 3243 subjects was determined by failure-time analysis during period of stable prevalence and incidence of infection after annual screening and chemotherapy in villages A–C. Time to infection is expressed as curves of infection-free survival over time. Time to infection was significantly ($P < .001$) longer for villages A and B than for C-1 and C-2. In addition, time to infection was significantly ($P < .001$) shorter for C-2 than for C-1. Children ages 7–13 years were infected significantly ($P < .001$) more rapidly than adults >14 years and children <7 years. Initial number of subjects in each age group: 0–6 years, 870; 7–13 years, 747; 14–35 years, 820; and >35 years, 806.

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**Figure 5.** Time to infection with *Schistosoma japonicum* stratified by age and infection status. A: Children ages 7–13 years; B: ages 14–35 years. Significant differences ($P < .001$) were seen in time to infection in subjects ages 14–35 years who were infected at enrollment and treated compared with subjects uninfected at time of enrollment. Numbers of subjects in each age group are in legend to figure 4.
objective of this study was to examine the impact of the Philippine National Control Program on schistosomiasis japonica, an approach for diagnosis similar to that used by the government was used in this study. 

Our study indicates that examination of a single stool sample for each subject missed 35% of lightly infected persons. These results suggest that the sensitivity for 2 Kato-Katz smears done on a single stool sample was relatively poor because of a high number of false-negative results, and thus the predictive value of a negative stool examination would be low. The incidence of infection would therefore have been underestimated during this 8-year study, and the impact of case finding and treatment would be significantly less than demonstrated. Nevertheless, when these data are examined in conjunction with the decrease in intensity of infection and the prevalence of schistosome-associated morbidity over time, these observations suggest that population-based chemotherapy had a significant impact on schistosomiasis japonica in these communities.

A major goal of population-based chemotherapy is to reduce schistosome-induced morbidity [19]. Hepatomegaly, a common morbid sign of schistosomiasis, is due to a granulomatous inflammatory host response to ectopically deposited eggs trapped in the perisinusoidal spaces of the liver [20]. In the first year of this study, hepatomegaly was found in 18% of infected subjects while liver enlargement was seen in 8.3% of uninfected subjects. These data suggest that hepatomegaly in this area in which schistosomiasis japonica is endemic was due largely to schistosomiasis japonica. Furthermore, the overall prevalence of hepatomegaly that included both infected and uninfected persons in these communities decreased from 12% in year 1 to 6% by year 5 and remained stable thereafter. This decrease was due to treatment of infected persons, since the age-specific prevalence of hepatomegaly among infected subjects was similar between year 1 and the last 3 years of the study. It is unlikely that any control program will successfully decrease the rate of hepatomegaly in a community to zero because of rapid reinfections with S. japonicum and because of the presence of other common hepatic diseases in rural Philippines, such as chronic hepatitis B and alcoholic liver disease.

The prevalence of schistosome-induced hepatomegaly in a community represents a balance of competing factors, including the development of new infections, the intensity of the infections, the rate of reinfection after treatment, and the host response to the parasite. For a population undergoing continual community-based chemotherapy, a balance will be established between the rate at which hepatomegaly develops following a primary infection or reinfection and the rate of reversal of hepatomegaly following successful treatment. In this study, we attempted to quantify the dynamics of development and reversibility of hepatomegaly in a human population undergoing intensive annual screening and treatment using failure-time analysis, an effective method to describe the occurrence of events over time [12].

Schistosome-induced hepatomegaly developed rapidly within 2–3 years in subjects who became reinfected but were left untreated. These subjects included persons in villages A and B whose treatment was deferred for 2 years in years 6 and 7 and infected persons who did not return for treatment until subsequent years. This finding led to discontinuation of the arm of the study that evaluated the impact of increasing the interval between community surveys in villages with low prevalences of infection.

Previous population-based studies have documented the beneficial effect of intensive chemotherapy on hepatosplenic enlargement in S. mansoni, for example, in Brazil [21]. In contrast, no studies have systematically examined the effect on morbidity if annual treatment was not maintained. Mathematical models that examined the effect of treatment on transmission of helminths predicted that “ideal” coverage and frequency of drug treatment for control of schistosomiasis mansoni was at intervals of 4 years [22]. The effect on morbidity, however, was not directly addressed, and similar models have not been developed for schistosomiasis japonica. Nevertheless, the current study suggests that in the Philippines, treatment with praziquantel every 3 years could result in persistent reductions in prevalence and intensity of infection in villages with low prevalences of schistosomiasis japonica, but such treatment could also result in unacceptable increases in the prevalence of hepatomegaly.

Fortunately, hepatic enlargement in schistosomiasis japonica, as demonstrated in the current study and in a similar study in China, was readily reversible with treatment [23]. Reversibility was independent of age. This may reflect the fact that hepatic enlargement is predominantly due to an egg-induced granulomatous inflammatory response that reverses with chemotherapy. Similar observations have been made in the mouse model [24]. Schistosome-induced periportal fibrosis, a common sequela of sustained hepatic inflammation, does not typically cause massive hepatic enlargement [25]. Thus, the lower prevalence of hepatomegaly observed in older adults suggests less granulomatous inflammation but does not address the degree of hepatic fibrosis. Ultrasonography suggests that the grade of schistosome-induced fibrosis increases with age and persists in persons who have had documented infection-free intervals for up to 8 years [26] (unpublished data).

The apparent disparity between the relatively low (18%) prevalence of hepatomegaly among infected subjects before the use of curative chemotherapy and the predicted frequency of development of new-onset hepatomegaly in infected subjects that were not treated (estimated to be >80% for those infected for >2 years, figure 2) strongly suggests the development of modulatory adjustments to chronic hepatic schistosome-induced inflammation in the infected and untreated population after years of sustained parasitism. The presence of this modulatory effect is further supported by the age-specific prevalence of hepatomegaly seen in the first year of the study. In this case, the prevalence of hepatomegaly peaked in the 10- to 14-year age group and then declined in older persons, suggesting modulation of hepatomegaly with increasing age. This effect has
also been demonstrated in chronically infected mice and is believed to be immunologically mediated [24]. Such an immunologic adjustment in schistosome-induced disease would represent a beneficial adaptation for S. japonicum-infected hosts faced with chronic parasitism [27, 28]. Furthermore, these data suggest that modulation of schistosome-associated hepatic disease was dramatically altered following curative chemotherapy. Further studies are needed to determine the long-term clinical impact of new-onset hepatomegaly in infected persons.

Population-based chemotherapy is the primary approach used to control schistosomiasis japonica in rural Philippines. Our results suggest that this strategy is successful in controlling the prevalence, incidence, and intensity of infection and, to a lesser extent, morbidity due to the parasite S. japonicum. These results also suggest a potential negative impact of population-based chemotherapy. If infection cannot be eradicated from the Philippines and morbidity rapidly develops in infected persons within 2–3 years, intensive yearly chemotherapy must be continued without interruption. If annual treatment is discontinued, a rapid increase in the prevalence of hepatomegaly would occur, as demonstrated in villages A and B in 1987–1989. The long-term clinical impact of new-onset hepatic enlargement in infected persons is currently unknown but needs to be evaluated.

These data also allowed us to determine if there was epidemiologic evidence for the presence of acquired resistance to reinfection with S. japonicum in a human population. Resistance to reinfection following curative chemotherapy has been demonstrated for S. mansoni and S. haematobium infections in humans [29–31]. This is based on the observations that the intensity of reinfection after treatment with schistosomiasis is age-dependent [29–33]. Water contact has been shown to decline in older persons, but this decrease cannot account for the marked reduction in the intensity of infection and therefore suggests development of resistance to reinfection over time. Furthermore, acquired resistance to reinfection is dependent on prior schistosome infections and therefore implies that the mechanism of resistance to reinfection following parasitologic cure is immunologically based [32]. The cellular and humoral responses for this acquired form of resistance in humans are, however, poorly defined [29].

Animal models have been helpful in the identification of potentially protective antigens and in the investigation of protective immune responses in experimental schistosomiasis [33]. Most antigens tested so far have been identified in S. mansoni, but in recent years, similar studies for schistosomiasis japonica have been done. For example, irradiated attenuated vaccines induced significant protection against S. japonicum infection in the laboratory and in livestock in field trials in China [34, 35]. Moreover, immunization with isolated antigens, such as paramyosin, induced significant immunity against infection with S. japonicum [36–38]. These studies are particularly important since S. japonicum is a zoonosis; immunization of bovines alone in countries in which the disease is endemic could significantly reduce transmission of schistosomiasis japonica to humans.

In the present study, we provide evidence for the development of acquired resistance in a human population chronically exposed to S. japonicum in the Philippines. Our data suggest that the risk of infection with S. japonicum was age-dependent and community-specific. Changes in the environment, such as the destruction of the piped water supply in village C, were associated with a significant change in the time to reinfection for the community as a whole.

In all communities, the time to infection in children <6 years of age was significantly longer than that observed for children ages 7–13. This may reflect less frequent exposure to infected water among children, especially those <3 years old. Time to infection was also significantly more rapid in children ages 7–13 years compared with older subjects. This suggests that if water exposure for both age groups was similar, these persons were more susceptible than older subjects to infection. This was the conclusion of a similar study of S. mansoni [29].

The most direct and compelling evidence for acquired resistance comes from the analysis of children stratified by age and infection status. Our data demonstrated a significant decrease in the risk of reinfection with S. japonicum in older persons (14–35 years old) who were infected at the time of entry into the study and treated compared with uninfected age-matched persons. This difference was clearly age-dependent, with resistance appearing to develop in subjects 14–35 years old but not in children <14 years old. Thus, prior infection was associated with significant resistance to reinfection with S. japonicum.

The magnitude of this resistance to reinfection can be demonstrated by comparison of the Kaplan-Meier plots (figure 5). For example, 30% of the uninfected subjects ages 14–35 became infected within 702 days. In contrast, it took 1100 days for 30% of subjects of similar age to become reinfected, a delay of 1.1 years. Resistance to reinfection after treatment is clearly partial and apparently of short duration in that by 6 years after entry in the study, the protection of prior infection was no longer evident.

These data suggest that children 7–13 years old were significantly more susceptible to infection with S. japonicum irrespective of a history of active infection. With increasing age, however, resistance to reinfection developed in subjects who were previously infected and treated for S. japonicum compared with subjects never infected with this parasite. This study provides the first direct demonstration in humans of acquired resistance to reinfection conferred by active infection with this schistosome species. It also suggests that resistance to reinfection may take as long as 10 years of chronic exposure and infection to develop but is lost within 5 years after successful chemotherapy.

The mechanism for the slow development of acquired resistance with age to S. japonicum is unknown. With S. mansoni, continued susceptibility to reinfection of young children is associated with high levels of “blocking” antibodies against...
carbohydrate epitopes expressed in eggs and young migrating larvae [39]. With time, these antibodies decline with age, allowing development of a more effective immunologic response. In addition, IgE levels increase progressively with age and significantly correlate with resistance to reinfection [40]. Thus, IgE may have a protective role against S. mansoni in humans. Similar mechanisms may also occur in S. japonicum.

Alternative explanations could explain these observations on reinfection. A decline in water contact with increasing age may result in a significant decrease in the rate of reinfection after treatment. We believe that reduced water contact is unlikely, since persons infected with S. japonicum at the time of entry into the study would, if anything, be expected to have increased exposure to infected water compared with uninfected subjects. Furthermore, water contact appears to be ubiquitous after the age of 4–6 years in these rice-farming communities. Studies on transmission of S. japonicum in which water contact risk is measured in terms of environmental endemicity and human behavior on an individual level are necessary to confirm these results and are currently ongoing.

Another explanation for these results is the differential sensitivity of Kato-Katz smears to detect S. japonicum infection between the 7- to 14-year and 14- to 35-year age groups. However, there are no data from other studies to support this suggestion. Alternatively, resistance to infection may simply reflect anatomic/mechanical blockage of migrating larvae due to hepatomegaly, as has been suggested in mice [41]. Whether such a process occurs in humans is unknown. However, our data suggest that the prevalence of hepatomegaly was greater in the 10- to 14-year age group, who had higher levels of infection, than in older persons, who had reduced rates of infection and hepatomegaly [9]. These data make this hypothesis less likely.

In conclusion, our study suggests that the current strategy of the national schistosomiasis control program in the Philippines will dramatically decrease the prevalence, incidence, and intensity of schistosomiasis and will result in a modest reduction in morbidity. However, transmission will not be eradicated. We speculate that an unexpected result of population-based chemotherapy will be to reduce the ability of the host to modulate egg-induced hepatic inflammation. This lack of modulation will be of no serious consequence to the health of a community, provided that the control program is maintained. If the national control program is ever stopped or dramatically curtailed, as occurred in 1984 with the withdrawal of international funding, then a modest increase in the rate of infection and a marked rebound in short-term morbidity would be expected to occur. Thus, it is essential that international support be used to build an infrastructure capable of maintaining intensive control efforts until newer approaches such as a vaccine in bovines or humans become available. Our studies also suggest that acquired resistance to reinfection with S. japonicum occurs in humans chronically exposed to this parasite in the Philippines. These epidemiologic observations in humans support experimental studies in animal models that demonstrate that the successful induction of protective immunity against S. japonicum infection is indeed possible [33–38]. Thus, vaccine development for both bovines and humans is important in schistosomiasis japonica since, despite intensive population-based chemotherapy, S. japonicum infection cannot be eradicated in the Philippines, so alternative approaches for control of this parasitic helminth are needed.

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