Assessing the WHO 50% Prevalence Threshold in School-Aged Children as Indication for Treatment of Urogenital Schistosomiasis in Adults in Central Nigeria

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Abstract.

Preventive chemotherapy with praziquantel is recommended in adults by the World Health Organization when prevalence of schistosomiasis in school-aged children (SAC) is ³ 50%. This study ascertained the value of this threshold in predicting prevalence and intensity of Schistosoma hematobium (SH) infection in adults in central Nigeria. We evaluated urogenital schistosomiasis prevalence in 1,164 adults: 659 adults in 12 communities where mean hematuria among SAC in 2008 was 26.6% and 505 adults in 7 communities where the mean hematuria among SAC in 2008 was 70.4%. No statistically significant differences were found between the two groups of adults in prevalence of hematuria, prevalence of SH eggs, or intensity of infections. We conclude that, in this setting, the SAC threshold is not useful for treatment decisions in adults. Given the increased risk of subtle morbidity or urogenital schistosomiasis as a risk factor for human immunodeficiency virus (HIV), more liberal treatment of adults with praziquantel is warranted.

INTRODUCTION

Current (2006) World Health Organization (WHO) guidelines for preventive chemotherapy (PCT) of Schistosomiasis call for targeted distribution of praziquantel (PZQ) based on the prevalence of the disease in school-aged children (SAC).[1] According to these guidelines, moderate-risk areas, where SAC prevalence is 10–49%, should limit mass PZQ treatment to SAC, whereas high-risk areas, with SAC prevalence of ³ 50%, should target both children and at-risk adults. At-risk adults who should receive PCT should range "from special groups (pregnant and lactating women; groups with occupations involving contact with infested water, such as fisherman, farmers, irrigation workers, or women in their domestic tasks) to entire communities

living in endemic areas" (ref. 1, p. 60).The rationale given for treating adults in high-risk communities defined by the SAC indicator group is that adults in these areas are at greater risk of developingmorbidity because of infection.[2]

The purpose of this study was to ascertain the value of the recommended [3] 50% SAC thresholds for predicting heavy infections with Schistosoma haematobium (SH) among adults in a large schistosomiasis control program in Nigeria.

METHODS

Study site.
Plateau and Nasarawa states are located in northcentral Nigeria, where both S. hematobium and S. mansoni are endemic with heterogeneous levels of prevalence that have been reported in previous publications.[3,4] Mass treatment of all SAC with PZQ (40 mg/kg orally, single dose) in these two states was started in 2008 after a study by Gutman and others[3] that showed that the presumptive treatment of SAC was less costly than assessing the entire area for S. haematobium (using urinary dipstick) and S. mansoni (using Kato stool examinations). Although this approach has reduced costs and provided treatment to all SAC, it goes against the WHO guidelines by not assessing the prevalence in all areas, and it inherently excludes the treatment of adults, because the 50% threshold is never determined. Because of these factors, we wanted to determine what the burden of schistosomiasis was among adults in these highrisk communities.

SAC mapping and sampling in 2008.
Communities included in this study were from four districts (called local government areas [LGAs]), where baseline prevalence of hematuria (a proxy for urogenital schistosomiasis) in children 10–14 years of age had been measured in 2008. School-based surveys followed standard mapping protocol for SH adapted from WHO. One government primary school was selected in each community in the LGAs. A random sample of children ages 10–14 years was asked to voluntarily provide a urine sample. To allow for error or refusal, at least 32 school children were selected and asked to participate. Children were called to assembly and separated according to age group. A total count of children ages 10–14 years was taken, and field teams applied the count to a pre-prepared table to identify the sampling interval required to provide the sample of a minimum of 32 children and a maximum of 47 children. After the sampling interval was determined, a random starting point between the first child and the sampling interval was selected using the preprepared random number from Microsoft Excel. In the case that the school had < 48 children in the desired age group, all children were asked to participate.

Survey of untreated adults in 2010.
The survey of untreated adults was conducted in July of 2010 after 3 years of SAConly PZQ treatment. A line list of the communities surveyed in 2008 was ranked in descending order according to their baseline prevalence of SAC hematuria. Communities were then aggregated into two groups: group 1 (moderate adult risk based on WHO guidelines), where baseline SAC prevalence was 20–49% (13 communities), and group 2 (high adult risk based on WHO guidelines), where baseline SAC prevalence was [3] 50% (8 communities). Group 1 showed a mean baseline SAC hematuria rate of 27.2% (range = 11.1–36.7), and group 2 had a mean baseline SAC hematuria rate of 71.1% (range = 52.2–80.6).

We estimated that a total sample size of at least 434 adults per group would allow for the detection of a difference of 10% in prevalence among adults between groups with the following assumptions: 0.05% significance level, 90% power, 10% prevalence among adults in group 1, and a design effect of two to account for potential correlation among data within communities. To achieve the desired sample size, we aimed to examine all adults in all 21 communities.

In each community surveyed, all households were listed and numbered according to geographic distribution as best as possible using the knowledge of village leaders. A random systematic sample of 24 households was selected from the list by calculating a sampling interval, taking a random starting household, and then selecting households from the list according to the interval. All adult residents in the community 20 years of age and older and present in selected households were assessed for urogenital schistosomiasis. After obtaining verbal consent, each adult was provided with a cup and asked to fill it with urine. Urine specimens were tested immediately for hematuria (rapid reagent strip test; Uripath by Plasmatec Laboratory Products Ltd., United Kingdom) and also filtered using syringe filtration for detection of S. hematobium eggs. The reagent strips were read after 1 minute against the jar label and recorded as negative, trace, +1, and +2 per manufacturer's instructions. We considered a reagent strip result of +1 or more as a positive indicator for hematuria. Urine filtration was conducted by passing 5 mL urine through a filter (Nylaflo membrane disc filters, 13-mm diameter, 20-mm pore size) using a syringe. The filter was removed from the holder, placed on a slide, stained with iodine, and examined microscopically at 40 +. SH eggs were identified and counted. We considered a finding of 1–24 eggs/5 mL as a light SH infection and ³ 25 eggs/5 mL as a sign of a heavy SH infection.

Data collection and analysis.
Two teams of one supervisor and four laboratory technicians collected data in all communities. Applied training on the use of the rapid reagent dipstick test, filtration and microscopy, sampling methodology, and data collection was provided to all team members before the survey. Individual data collection forms were used to collect sex, age, occupation, and test results, and they were compared with village registers. Data were compared with village PCT registers, which list all residents' names, ages, sex, and occupation by household. All data were doubleentered, compared for errors, and corrected. c2 tests, 95% confidence intervals (CIs), odds ratios (ORs), and multivariant analysis were done using SAS version 9.2 (SAS Institute Inc., Cary, NC). A comparison of overall prevalence and intensity of infection between the two groups was conducted using Pearson's c2 statistic. A P value of < 0.05 for the c2 value was considered a statistically significant difference in prevalence between groups.

Ethical considerations.
This study was considered by the Emory Institutional Review Board (IRB) to be part of an ongoing evaluation of the schistosomiasis control program of the Nigeria Federal Ministry of Health, which has been previously approved under Emory University IRB protocol IRB00002373. Informed oral consent was obtained before specimen collection. All persons testing positive for hematuria or having eggs in urine were offered treatment with PZQ (40 mg/kg orally in a single dose) according to national program guidelines.

RESULTS

We were unable to reach two communities during the survey (one in each group) because of civil unrest/security issues. Therefore, adults were examined from 11 of 12 moderate adult risk communities (group 1) and 8 of 9 high adult risk communities (group 2). A total of 1,164 adults were examined of 1,287 registered in the sample households (90% response rate): 602 adults in group 1 and 562 adults in group 2. Respondents were 54.4% female and had a mean age of 32.2 years (Table 1). There was no significant difference in group composition in either age or sex. Most respondents reported their occupation as farmers (39.6% surveyed versus 41% registered) or housewife (25.6% surveyed versus 25% registered). Although no significant differences between the two groups existed in occupation according to registers, significant differences among respondents were reported during the survey interviews: group 1 (moderate risk for adults) contained more business workers (11.3% versus 6.3%, $P < 0.01$) and civil servants (4.4% versus 1.8%, $P < 0.01$), whereas group 2 (high adult risk) contained more fishermen (1.9% versus 0.1%, $P < 0.01$). Residents in both groups were equally likely to participate in the survey (90.4% versus 90.5%, $P = 0.95$).

No statistical difference was observed in adults between the two groups for any of the infection indicators assessed: prevalence of eggs, prevalence of hematuria, and number of eggs per 5 mL urine (Tables 1 and 2). Overall, the prevalence of infection (eggs) among all adults examined was 18.7% (95% CI = 11.5–26.0%), with 17.4% (95% CI = 6.4–28.5%) in group 1 and 20.1% (95% CI = 11.1–29.1%) in group 2 ($P = 0.698$). The overall hematuria prevalence was 18.0% (95% CI = 11.7–24.2%), with 18.1% (95% CI = 7.7–28.5%) in group 1 and 17.8% (95% CI = 11.4–24.2%) in group 2 ($P = 0.957$). The mean egg count among positive specimens was 2.4/5 mL (range = 1–30). The prevalence of light infections (i.e., 1–24 eggs/5 mL) was 11.8% (95% CI = 10.0–13.8%) overall, 10.3% (95% CI = 8.0–13.0%) in group 1, and 13.5% (95% CI = 10.8–16.6%) in group 2 ($P = 0.089$). Intense infection ($\geq$ 25 eggs/5 mL) was found in only one adult: 0.08% (95% CI = 0.0–0.4) overall, 0.0% (95% CI = 0.0–0.6) in group 1, and 0.2% (95% CI = 0.0–1.0) in group 2 ($P = 0.3$). The prevalence of hematuria, defined as a dipstick result of $\geq$ 2+, was 11.7% (95% CI = 7.4–16.0%) among all adults, 13.0% (95% CI = 5.1–20.8%) in group 1, and 10.3% (95% CI = 7.8–12.8%) in group 2 ($P = 0.4652$).

View this table:	TABLE 1
[in this window] [in a new window]	Population and sample group characteristics

View this table:	TABLE 2
[in this window] [in a new window]	Prevalence, intensity, and hematuria prevalence in adult group 1 (SAC 20-49%) compared with adult group 2 (SAC ≥ 50%) based on original SAC category

Other factors affecting adult's infection status irrespective of risk groups 1 and 2 are shown in Table 3. Males were not more likely than females to have hematuria (OR = 1.2, 95% CI = 0.9–1.6, P = 0.248), but they were more likely than females to have infections (OR = 2.0, 95% CI = 1.4– 2.9, P < 0.01). Young adults between 20 and 29 years had significantly higher rates of hematuria than older adults (OR= 1.2, 95%CI = 0.9–1.6, P < 0.05) but did not differ in infection rates (OR = 1.4, 95%CI = 0.96–2.1, P = 0.084). An individual adult's hematuria status was not associated with children in the sample household reporting having taken PZQ, presence of a latrine at the household level, and baseline SAC classification of the community in multivariate analysis.

| View this table: [in this window] [in a new window] | TABLE 3 General characteristics of total adult sample | |

DISCUSSION

We were unable to find any statistical difference in SH infection (hematuria, eggs in urine, or light or heavy infections) among adults living in communities above and below the critical SAC PCT indicator group threshold of 50% prevalence. Our results suggest that, in this particular setting in central Nigeria, the 50% SAC threshold does not predict greater numbers of adults living with high SH infection risk, because the high-risk prevalence (20%; 95% CI = 11.1–29.1%) and intensity of infections (mean = 2.75/5 mL) were low. Stated another way, our findings suggest that adults in both groups 1 (moderate adult risk) and 2 (high adult risk) are equally at risk of developing morbidity associated with Schistosomiasis hematobium infection, and therefore, there is no reason to stratify program operations based on the 50% threshold. On one hand, these data support our current approach of providing PZQ treatment only to SAC. On the other hand, if PZQ availability and costs were not an issue, the data support providing universal treatment (e.g., treating all eligible adults as well as children).

As recognized by the current WHO guidelines, growing evidence of the effects of schistosomiasis infection on adult morbidity points to a greater need for inclusion of adults in schistosomiasis PCT treatment programs. There are several arguments in support of treating adults with SH infection. Although heavy infection prevalence (defined as percentage of persons having ³ 25 eggs/5 mL urine) in this study was very low (group 1 = 0.0%; group 2 = 1.0%), strong arguments have been made in recent years about the need to reduce the effects of subtle morbidity from schistosomiasis that result from low-intensity infections. Such infection limits the productivity and wellbeing of adults.[5,6] As noted in the works by King and others,[5,6] anemia, abdominal pain, exercise intolerance, and lowered work performance resulting from lowintensity infections may play a greater role in daily life than previously thought. Also, there is growing discussion around elimination of schistosomiasis and the role that adults may play in ongoing transmission.[7,8] Any thought of Schistosomiasis elimination will need to consider that adults certainly contribute to community transmission and need to be included in the mass treatment

and health education/behavioral change program. Additionally, the role of urogenital Schistosomiasis in human immunodeficiency virus (HIV) and possibly, human pampillomavirus (HPV) infection has recently been recognized. [9–12] Disruption of the genital tract epithelium caused by S. haematobium eggs has been associated with increased risk for acquiring HIV infection. Some studies have suggested that the SH infection can result in increased viral loads of HIV or HPV, which could result in the increased ability of the infected persons to transmit these viruses to others.[10,13]

A very interesting finding in our study was that the male occupations differed between the two groups in our study. Group 2 had more high-risk occupations (fishermen and farmers) than did group 1 (which had more businessmen and civil servants). However, SH infection rates were not different. This finding goes against many studies, which show clear associations of infection with water exposure associated with fishing and farming.

There are several limitations to this study. One limitation was that our methods for determining intensity of infection examined one-half (5 mL urine) of the WHO-recommended 10 mL. In our analysis, we corrected for the WHO standard of light and heavy infections (1–49 eggs/10 mL and ³ 50 eggs/ 10 mL, respectively) by adjusting our standards by one-half. This adjustment could potentially affect the number of light (in particular) or heavy infections found, but it would not affect or bias our ability to compare our findings between the two groups.

The lower-limit WHO thresholds for initiating mass drug administration among SAC changed during the course of our work in Nigeria, decreasing from 20% in 1997 to 10% in 2006. As a result, our baseline data were for the 20–50% strata rather than the current 10–50% cutoff. Conceivably, adding the 10–19% communities could have resulted in lowering the infection rates among adults in the moderate-risk group, and a difference, perhaps, would have been observed in adult infection rates between the two groups. Our purpose, however, was to identify the power of the 50% threshold rather than the moderate-risk group as a whole. We allocated communities into the two risk groups based on a 2008 SAC survey involving random selection of only 30– 40 school children. Therefore, another potential problem could be misclassification bias of communities into the highor moderate-risk groups because of the small SAC sample size. The likelihood of this misclassification, however, would be low given the considerable difference between the SAC baseline infection in the two groups (26.6% versus 70.4%).

One of the key programmatic challenges for implementing a schistosomiasis control program has been the need to stratify areas or communities into two treatment strategies: treat all SAC or treat the entire community (e.g., all SAC and at-risk adults). Surveys to identify the mean prevalence of Schistosomiasis and thereby, determine which treatment strategy to use can be costly and add substantially to the total cost of treatment programs.[14–17] The focal nature of the infection adds to the complexity of a sampling scheme to develop a two-tier treatment approach. There have been different approaches to such stratification outside of sub-Saharan Africa. For example, in endemic areas of China, where the strategy is to control and eventually interrupt transmission of S. japonicum, all people ages 5–65 years, regardless of community infection status, are treated.[18] In Egypt, PZQ distribution evolved over time. Mass treatment in 1997 was given in all

communities with ³ 20% SAC prevalence. This SAC threshold gradually decreased to ³ 10% in 1999, ³ 5% in 2000, ³ 3.5% in 2002, and ³ 3% in 2003.[19]

In January of 2012, Merck KGgA (E-Merck) pledged to increase its PZQ donation from 50 million to 250 million tablets annually for as long as needed. This donation will greatly increase the availability of PZQ globally, but it is still less than one-half of the more than 500 million tablets needed annually to treat everyone at risk under the current thresholds for treatment.[20] Accordingly, consideration will still need to be given to the cost and availability of PZQ, and rationing of PZQ to SAC will likely continue to occur based on a stratification scheme according to endemicity because of PZQ shortages.

In conclusion, PCT with PZQ is recommended in adults by the WHO when prevalence of schistosomiasis in SAC is ³ 50%. However, in our project area in central Nigeria, we found no evidence to support using this threshold to alter our PCT approach that is currently aimed only at universal treatment of SAC. We suggest that other programs conduct similar simple operational research assessments to adaptWHO guidelines to their particular circumstances. However, we strongly support a policy of enhanced PZQ distribution to include adults where funding and PZQ supplies permit.

Acknowledgments:

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