Evidence Against Rapid Emergence of Praziquantel Resistance in *Schistosoma haematobium*, Kenya

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We examined the long-term efficacy of praziquantel against *Schistosoma haematobium*, the causative agent of urinary schistosomiasis, during a school-based treatment program in the Msambweni area of Coast Province, Kenya, where the disease is highly endemic. Our results, derived from treating 4,031 of 7,641 children from 1984 to 1993, indicate substantial year-to-year variation in drug efficacy. However, the pattern of this variation was not consistent with primary or progressive emergence of praziquantel resistance. Mathematical modeling indicated that, at current treatment rates, praziquantel resistance will likely take 10 or more years to emerge.
Cleveland and the Ministry of Health, Kenya, case-finding was performed by school-based and follow-up village surveys. Details of the protocols have been published (25-27). In 1984, the initial treatment year, S. haematobium-infected children were randomly assigned to groups for treatment with either praziquantel (Biltricide, Bayer, Leverkusen, Germany), 40 mg/kg once a year, or metrifonate (Bilarcil, Bayer), 10 mg/kg three times a year. In years 2 and 3, the initial treatment was repeated, independent of parasitologic findings. New entrants to the study were assigned randomly to either the praziquantel or metrifonate treatment groups, according to the original 1984 protocol. In 1987, half the 1984 cohort, treated either with praziquantel or with metrifonate, was randomized to receive a single dose of metrifonate, 10 mg/kg, as a “consolidation” treatment. After a 2-year hiatus, annual treatment was resumed in 1989 to 1991; during this period, only children in whose urine samples eggs were identified (egg-positive children) were treated with praziquantel alone.

Infection status was determined by Nuclepore (Whatman, Kent, UK) filtration of two 10-mL samples from stirred midday urine specimens. Infection-associated disease was determined by physical examination, dipstick urine examination for hematuria and proteinuria, and ultrasound examination of the kidneys and bladder (25). Clinical and parasitologic testing was performed each year. Results were coded and entered for analysis in databases at Case Western Reserve University and the Kenyan Ministry of Health.

Data Analysis

Results of annual treatments were scored as “cure” for patients whose status changed from egg-positive to egg-negative, “noncure” for those whose status remained egg-positive, and “infected or reinfected” for those whose status changed from egg-negative to egg-positive between yearly examinations. Because of the skewed distribution of egg counts in the infected population, the effects of treatment on average intensity of infection were assessed by determining the change in geometric mean egg count between examinations. Differences between outcome rates were assessed by the chi-square test with Yates’ correction or Fisher’s exact test.

Mathematical Modeling

The potential for development of praziquantel resistance in the study population was first estimated by the Hardy-Weinberg equilibrium analysis (28). We then used a deterministic, simultaneous differential equation model of helminth resistance (Appendix, 29). This more advanced model takes into account the skewed (negative binomial) distribution of number of worms in human populations, the obligate sexual reproduction of the parasites, and a possible decrease in fecundity as a result of parasite crowding in heavily infected humans. The model provides estimates of average level of infection in the study population, as well as the prevalence and density of resistant worms over time. Results are shown as three-dimensional graphs of mean numbers of worms over time (20 years), as a function of annual community drug use (p), and the reproductive fitness of resistant parasites. Treatment efficacy and aggregation constants for infection (k) were derived from our study area.

Results

Yearly Efficacy of Praziquantel

During 1984 to 1992, we observed substantial year-to-year variations in cure rates (conversion from egg-positive to egg-negative status on urine Nuclepore filtration examination) for both praziquantel and metrifonate (Table 1). The response to metrifonate treatment declined each year, from 79% in 1984 to 47% in 1987 (p <0.001, Figure 1); in contrast, we observed no consistent downward trend in response to praziquantel treatment, despite repeated use of the drug in many patients (Figures 1 and 2). However, the response to praziquantel varied significantly from year to year (p <0.001), from a cure rate of 96% in 1990 (year 7 of the project) to a cure rate of 65% in 1986 (year 3, p <0.001). This level of efficacy was within the previous range of S. haematobium cure rates, both in Coast Province and elsewhere in Africa (Table 2). In suppression of infection intensity, the praziquantel-mediated reduction of mean S. haematobium egg counts was consistently >83% for all years of observation.

Impact of Repeated Treatment

In both the study periods during which repeated, annual praziquantel treatment was
used (1984-1987 and 1989-1993), the observed
cure rate for egg-positive children increased in
year 2 of treatment, then decreased in year 3
(Figure 1). The number of egg-positive children
remaining to be treated in successive years was
small, and this sample did not have sufficient
statistical power to determine whether the year 3
decrease in praziquantel response was due to
fluctuations in transmission (30), progressive
selection of patients at high risk for exposure to
S. haematobium (27,31), or gradual selection of
praziquantel-resistant parasites.

Table 1. Effectiveness of praziquantel in eliminating Schistosoma haematobium infection, Msambweni, Coast Province,
Kenya, 1984-1992

<table>
<thead>
<tr>
<th>Patient’s infection and Year treated with PZQ or metrifonate</th>
<th>Prevalence of infection at 12 months after treatment (interval change in geometric mean of (egg count +1) for group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg-positive urine, given PZQ, never previously treated</td>
<td>17%</td>
</tr>
<tr>
<td>n = 981</td>
<td>33 to 1.5</td>
</tr>
<tr>
<td>Egg-positive urine, given PZQ, had &gt;=1 PZQ treatments</td>
<td>-</td>
</tr>
<tr>
<td>n = 111</td>
<td>10 to 1.5</td>
</tr>
<tr>
<td>All egg-positive, PZQ-treated patients</td>
<td>17%</td>
</tr>
<tr>
<td>n = 981</td>
<td>15 to 1.5</td>
</tr>
<tr>
<td>Infection rate (egg - to egg + conversion)</td>
<td>15%</td>
</tr>
<tr>
<td>All patients, treated and untreated</td>
<td>18%</td>
</tr>
</tbody>
</table>

PZQ = praziquantel.

Figure 1. Yearly efficacy of drug therapy. Results of praziquantel treatment (solid bars) or metrifonate treatment (shaded bars) for Schistosoma haematobium infection in the Msambweni area during 1984 to 1992. Cure rates (conversion from egg-positive to egg-negative urine in annual follow-up testing) are shown for all egg-positive cases, by year of treatment. Only metrifonate therapy was given in 1987, and no treatment was given in 1988.

Figure 2. Efficacy of praziquantel therapy for Schistosoma haematobium according to prior treatment status. Solid bars indicate yearly cure rates for patients receiving their first praziquantel treatment. Hatched bars indicate cure rates for children with a history of prior praziquantel treatment. No significant differences in efficacy were noted in any of the years studied (1985-1991).
Given the incomplete efficacy of praziquantel in eradicating infection (6) and the single annual follow-up, our study design could not distinguish reinfection from possible drug failure. Therefore, we used several indirect variables to estimate ongoing praziquantel efficacy: the level of persistent egg-positivity at 1 year after praziquantel treatment, compared with rates of new infection (egg-negative to egg-positive conversion) each year; the efficacy of the drug in children receiving a second, third, or fourth dose, compared with efficacy in children receiving a first dose; and the efficacy of the drug in children who remained egg-positive after their first dose compared with efficacy in children whose infections cleared but who subsequently became reinfected.

Persistent Infection vs. Reinfection
The yearly efficacy of praziquantel treatment and infection or reinfection rates (egg-negative to egg-positive conversion) were compiled for the study population (Table 1). Yearly infection or reinfection rates varied from 15% in 1984 to 1985 to a low of 9% in 1985 to 1986 and a high of 21% in 1991 to 1992 (average 13%). Infection rates for children initially treated with praziquantel who subsequently missed 1 year or more of treatment were 22% to 34% in subsequent surveys 2 to 4 years later. These rates suggested a time-dependent average accumulation of reinfection at an annual rate of 9% to 15%. The high transmission levels in 1991 to 1992 (21% new infection or reinfection) may explain the apparent decrease in praziquantel efficacy during this 12-month period. However, estimated transmission did not explain the decreased efficacy seen in 1986 to 1987, when the population egg-negative to -positive conversion rate was only 11%.

Efficacy of Retreatment with Praziquantel
To examine whether an increasing core of resistant infection might account for the higher post-treatment prevalence after year 2 of treatment, we compared the relative annual efficacy in egg-positive patients who received praziquantel for the first time with efficacy in patients receiving their second, third, or fourth treatments. We found that after the first cycle of treatment, i.e., from 1985 on, praziquantel-mediated cure rates did not differ for patients with first-time treatment and those with a history of praziquantel treatment (Figure 2). We further examined the response to second, third, and fourth treatments in patients who did not become egg-negative after their first dose compared with efficacy in children whose infections cleared but who subsequently became reinfected.

Discussion
Without clear evidence of emerging resistance in our treated population, we considered
Figure 3. Extra doses needed to cure Schistosoma haematobium infection in 1984-entry cohort children who were not cured with a first dose of praziquantel (initial nonresponse, N=123, top bar) compared with doses needed to cure children reinfected after successful praziquantel treatment (reinfected post-cure, N=36, bottom bar). The filled areas in each bar indicate percentage of each group requiring one (solid), two (hatched), or three (shaded) more doses of praziquantel to become egg negative. No significant differences were observed between the two groups in age, sex, or cure rates.

Two related questions: Why was resistance not observed, and when might it be expected to emerge under the field conditions tested? To answer these questions, we turned to mathematical models of inheritance of drug resistance.

A number of factors may account for the lack of evidence of praziquantel resistance in the Msambweni project. Although S. haematobium resistance to praziquantel is likely to emerge at some future time, the interval required for detection of resistance may be much longer than our 8-year observation period. An effective praziquantel-resistance mutation may be so rare that the number of generations required for it to become the dominant phenotype has not yet occurred. In Egypt, for example, apparently resistant strains of S. mansoni are emerging >10 years after widespread availability of praziquantel treatment (32). For a single resistance gene mutation beginning at frequency of $10^{-6}$, a Hardy-Weinberg equilibrium analysis (28) predicts it would take eight or more generations for the resistant phenotype to become clinically detectable (i.e., 25% to 50% of worms) at the community treatment rates used in this study, if the resistance gene heterozygotes are fully resistant to treatment (i.e., a dominant trait [Figure 4a]). In our study, we estimate that 25% to 50% of infections were treated, but because the targeted

Figure 4. a. Hardy-Weinberg equilibrium analysis of the increase in resistance gene frequency in a parasite population where the initial R gene frequency is $10^{-6}$, heterozygotes and R gene homozygotes are fully resistant, and 75% of susceptible worms are lost to treatment each generation. b. As in a, but 40% of heterozygotes are lost to treatment each generation. c. As in a, but 99% of resistant homozygotes do not survive to reproduce.
school-age groups have the highest numbers of worms, 50% to 75% of worms may have been exposed to praziquantel. Emergence times for the resistance phenotype are longer if heterozygotes remain fully or partially susceptible to the drug (11 generations for 25% heterozygote loss after treatment and 14 to 18 generations for 50% heterozygote losses) and only the homozygotes are fully resistant (Figure 4b). Given the seasonal nature of rainfall and water exposure, the requirement of two sexes for schistosome reproduction, and the uneven aggregation of worms in the human population, the effective generation time for *S. haematobium* is likely to be at least 6 to 12 months, so we observed no more than 8 to 16 generations; our observation period may have been too short to identify praziquantel resistance. Our annual follow-up was an insensitive means to detect drug failure due to resistance. However, under the pressure of continued praziquantel treatment in the community, if resistant worms are fully fit, rapid predominance of resistant strains would be expected (Figure 4).

Praziquantel failure on initial treatment in *S. mansoni*-endemic areas of Senegal suggests primary resistance to praziquantel (16,18) and a high prevalence of resistance genes in the local *S. mansoni* strain (21,33,34). More recent reports indicate, however, that in this area of Senegal, retreatment after 40 days adequately reduces infection levels and achieves better cure rates (19). The latter results suggest that immature schistosomes, which are known not to be susceptible to praziquantel, are typically present in Senegalese patients at the time of treatment. If the treated patient has been recently exposed to infection (<6 weeks ago) in an area with continuous—rather than seasonal—transmission, apparent treatment failure may be observed when unaffected juvenile worms reach maturity and pass eggs several weeks after praziquantel treatment (14). Annual reinfection rates for *S. haematobium* may be high in some areas, such as Niger (35), and post-treatment infection detected after a single round of therapy should not be immediately interpreted as evidence of praziquantel resistance.

Nevertheless, animal studies of *S. mansoni* strains from Senegal indicate they are less sensitive to praziquantel than strains from other parts of the world (21,33,34). There is another explanation for an apparent low-level prevalence of drug resistance that fails to predominate in the parasite population: if a praziquantel-resistance mutation compromises reproductive fitness, the homozygous, fully resistant worm will never predominate. Instead, under the pressure of continued treatment, the resistance gene will achieve a stable-equilibrium share of the worm population, at a level dependent on its lower survival efficiency relative to that of the praziquantel-sensitive genotype (Figure 4c). This situation is analogous to the effect of the sickle cell-hemoglobin gene in human populations exposed to malaria.

Another possible factor likely to be slowing the emergence of praziquantel resistance in *Schistosoma* is the parasite's obligate dioecious sexual reproduction. Unlike drug-resistant bacteria, praziquantel-resistant schistosomes must find a mate of the opposite sex to reproduce, which requires a sufficient density of human infection. In a disease-endemic area where most of the population has been treated, the initial heavy loss of susceptible worms (>80%) may actually reduce mean number of worms sufficiently (i.e., to fewer than one male and one female per host) to prevent most resistant worms from finding suitable mates (29). Worm distribution is highly aggregated in the human population, with most (75%) patients having light infections and a small proportion (approximately 5%) having heavy infections. Heavy infection can result in reduced worm fecundity, slowing the production of eggs and thus the transmission of genes from a resistant worm, even though the chances of mating are enhanced. After treatment, the reduced number of worms in a heavily infected human could increase fecundity, so the net effect of treatment on praziquantel-resistance gene transmission would be difficult to predict. In an age-targeted program such as ours, praziquantel-sensitive parasites would also persist in the untreated adult and infant human subpopulations, slowing the dominance of drug resistance gene(s). This would occur by allowing interbreeding of resistant and susceptible worms in host locations not having the environmental pressure (i.e., praziquantel treatment) that favors the resistance gene.

Using a dynamic model of parasite transmission that accounts for these reproductive features of macroparasite transmission (Appendix), we examined the impact of treatment coverage and duration of control programs on the emergence of
resistant infection, to estimate the time required for drug failure. We also examined the impact of varying reproductive fitness of the resistant worms on the time to recrudescence of infection. Figures 5 and 6 show the predicted recrudescence of infection over a 20-year period, as influenced by treatment coverage and by reproductive fitness of resistant worms. Both simulations indicate at least an 8- to 10-year delay in the return of infection to pretreatment levels. This delay is especially noted if treatment coverage is incomplete (Figure 5) and resistant parasites are less reproductively fit than susceptible ones (Figure 6). The model further indicates that under the conditions of our program (targeted mass treatment, with 25% to 75% of infections praziquantel-treated), resistance becomes clinically apparent (>50% resistant worms) only after a period years longer than that we were able to observe.

In our model, we assumed an effective spontaneous mutation rate for praziquantel resistance of $10^{-6}$. Recent work by Moxon and colleagues (36-38) on the evolution of bacterial pathogens indicates that genetic mutation becomes accelerated (i.e., nonrandom) in a subset of organisms under environmental stress, such as drug pressure. The "hypermutable" phenotype prevails under these rapidly changing conditions because of its ability to adapt quickly to the new environment. Rapid genetic diversification is enhanced by simultaneous modular changes in DNA, which are facilitated by the presence of multiple copies of critical genes, transposons, and repeat regions or Z-DNA boundaries flanking key intron/exon boundaries (39). Higher organisms, such as schistosomes, are likely to use similar mechanisms in adaptation. Drake (40) has estimated that the effective spontaneous mutation rate per genome per sexual generation may be as high as $10^{-2}$ for the nematode *C. elegans* and $10^{-1}$ for the insect *Drosophila*. In sensitivity analysis of our differential model, reducing the mutation rate from $10^{-6}$ to $10^{-1}$ in our base case (50% coverage with 85% efficacy) reduced the expected time to emergence of resistance from 10 to 7 years. At higher levels of drug use (90%-100% coverage), the time to resistance was reduced from 7 to 5 years at the highest mutation rate ($10^{-1}$). This effect is not as dramatic as would be predicted by the simpler Hardy-Weinberg model.
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(i.e., a reduction from 14 to 3 generations for dominance of resistance), apparently because of the retarding effects of aggregation and mating on emergence of new genotypes.

In summary, our results indicate that significant resistance to praziquantel treatment had not emerged in S. haematobium in the Msambweni area as of 1991. As noted since its first use, praziquantel treatment was not 100% effective in eliminating infection (41). It was, however, reliably capable of suppressing intensity of infection in each of six rounds of treatment spaced over 8 years. These findings, together with our modeling analysis, support targeted use of chemotherapy for disease control in S. haematobium-endemic populations (1,26,42-44). In our program, praziquantel treatment was focused only on schoolchildren, the subpopulation having the highest numbers of worms (26,27). Higher treatment coverage increases evolutionary pressure on the schistosome population and hastens emergence of resistance. The limited coverage of a targeted (vs. mass-treatment) program may have reduced the tendency for resistance to emerge, compared with the experience reported for S. mansoni in Egypt (32).

For the treated Msambweni population, the benefits of treatment appeared to be maximal after 2 years of repeated yearly treatment (26,27). After this, a 2- to 3-year interval may be sufficient to maintain effective suppression of infection and disease (27). Because reduced exposure to the drug slows the emergence of drug resistance, the efficacy of longer intertreatment intervals in suppressing S. haematobium-related disease should be studied. Although efficacy should be maintained for a number of years, regular monitoring of drug efficacy is appropriate for all long-term praziquantel-based control programs (14). Emergence of praziquantel resistance should be anticipated within 10 to 20 years, and continued antischistosomal drug development should be pursued.

Acknowledgments
We thank the staff of the Division of Vector Borne Diseases, Ministry of Health, Kenya, and the students, residents, and faculty of Case Western Reserve University who worked to make the Msambweni Study a success; the people of the Msambweni area of Kwale District for their enthusiastic participation; and Daren Austin for his description and helpful discussions of macroparasite resistance models.

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References
Appendix

The following system of differential equations was used to model the level of schistosome infection and prevalence of resistant worms in the treated study population, where

- \( \sigma \) is the number of sensitive schistosomes per host,
- \( \rho \) is the number of resistant schistosomes per host, and
- \( \sigma + \rho = M \), the mean number of worms per host.

If \( p \) = the proportion of treated infections each year, and \( h \) = the efficacy of one course of treatment, then \( c = -\ln (1 - ph) \) is the relative increase in the per capita death rate of sensitive worms due to treatment.

The basic death rate for sensitive and resistant parasites is an aggregate function of parasite and host death rates, represented in the equations as

\[
\gamma_s = \frac{1}{\text{sensitive parasite lifespan} + \text{host lifespan}}
\]

and

\[
\gamma_r = \frac{1}{\text{resistant parasite lifespan} + \text{host lifespan}}
\]

\( R_0 \) represents the basic reproductive rate of the susceptible worm. If \( \phi \) = the relative loss of reproductive fitness of the resistant phenotype (with value from 0 to 1), then \( R_{0r} = R_0 (1 - \phi) \). \( \Psi \) represents the spontaneous mutation rate of resistant worms. To reflect the impact of obligate sexual mating and unequal distribution of worms among hosts, \( F \) is a fecundity expression where

- \( \Psi \) = the mating probability,
- \( z \) = the density-dependent effect on worm fecundity, and
- \( k \) = the aggregation constant of the negative binomial distribution of worms, such that

\[
F(\sigma + \rho) = \Psi [1 + (\sigma + \rho) \left( \frac{1 - z}{k} \right) ^{(\sigma + 1)}]
\]

Then, along the lines of equation 17.5 of Anderson and May (29) for repeated treatment,

\[
\frac{d\sigma}{dt} = \gamma_s \cdot \sigma \cdot \left[ R_{0r} \cdot F(\sigma + \rho) - 1 - \frac{c}{\gamma_s} \right]
\]

and assuming resistant parasites to be completely unaffected by treatment,

\[
\frac{d\rho}{dt} = \gamma_r \cdot \rho \cdot (R_{0r} \cdot F(\sigma + \rho) - 1) + \chi \cdot p \cdot \sigma
\]

For the numerical analysis of these equations, we used the ODE solver of MathCAD (MathSoft, Inc., Cambridge MA) based on the Runge-Kutta estimation with 1,000 steps for a model time span of 20 years.

Initial variable estimates were taken from our field data (treatment coverage among total infected population, \( p = 0.25 \) to 0.75; treatment efficacy, \( h = .65 \) to .95; aggregation constant, \( k = 0.067 \); host lifespan = 50 years) or from previously published estimates for S. haematobium biology (\( R_0 = 2 \) to 4; parasite lifespan = 3 to 5 years; density effect on fecundity, \( z = 0.96 \) to 0.99) (29).
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\begin{align*}
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\rho & \text{ is the number of resistant schistosomes per host, and} \\
\sigma + \rho & = M, \text{ the mean number of worms per host.} \\
\text{If } p & \text{ = the proportion of treated infections each year, and} \\
h & \text{ = the efficacy of one course of treatment, then}
\end{align*}
c = - ln (1 - ph) is the relative increase in the per capita death rate of sensitive worms due to treatment. The basic death rate for sensitive and resistant parasites is an aggregate function of parasite and host death rates, represented in the equations as

$$\gamma_r = \frac{1}{\text{resistant parasite lifespan}} + \frac{1}{\text{host lifespan}}$$

and

$$\gamma_s = \frac{1}{\text{sensitive parasite lifespan}} + \frac{1}{\text{host lifespan}}$$

$R_0$ represents the basic reproductive rate of the susceptible worm. If $\square = \text{the relative loss of reproductive fitness of the resistant phenotype (with value from 0 to 1), then}$

$$R_{0r} = R_0 (1 - \square).$$

represents the spontaneous mutation rate of resistant worms. To reflect the impact of obligate sexual mating and unequal distribution of worms among hosts, $F$ is a fecundity expression where

$$\psi = \text{the mating probability},$$

$$z = \text{the density-dependent effect on worm fecundity, and}$$

$$k = \text{the aggregation constant of the negative binomial distribution of worms},$$

$$F (\sigma + \rho) = \Psi \left[ 1 + (\sigma + \rho) \frac{(1-z)}{k} \right]^{(\sigma+1)}$$

such that
Then, along the lines of equation 17.5 of Anderson and May (29) for repeated treatment, and assuming resistant parasites to be completely unaffected by treatment,

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