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

To the Editor: The key issue in the development of drug resistance in parasitic helminths that do not multiply in their final host is the proportion of worms that remain in refugia (i.e., that are not exposed to the drug) relative to the number that are exposed but survive treatment (1). If the latter population is relatively large (as might occur, for example, after mass rather than targeted treatment), the worms that survive therapy could make a substantial contribution to the gene pool of the next generation, thus increasing the likelihood that resistance would develop. Since only a relatively small part of the population in Msambweni area of the Coast Province was treated by King et al. (2), it would be surprising if resistance had emerged.

If a predictive model is to work well, information should be available about the actual percentage of worms that already have genes for resistance. For example, in some communities in Kenya oxamniquine-resistant worms were relatively common before the drug had been used widely (3). The same may be true for praziquantel resistance in *Schistosoma mansoni* in Senegal (4-6). The large variation in response of *S. haematobium* found in field trials (Table 2 in [2]) suggests that genes for resistance to praziquantel could already be present in some areas. Until there are polymerase chain reaction probes for praziquantel resistance, the prevalence of genes for resistance to praziquantel could be estimated by giving two—or preferably three—treatments of praziquantel at monthly intervals and determining the reduction in egg counts after each round of treatment. Resistance could be confirmed through infection and treatment of rodents with isolates from uncured patients or by a simple test measuring the response of miracidia to praziquantel (7). With this information, it should be possible to make realistic predictions about the development of praziquantel resistance.

Although King and colleagues suggest the use of targeted treatment, it would perhaps be unfortunate if the optimistic-sounding title of their paper encouraged the mass use of praziquantel in the belief that resistance will not develop rapidly. This hope cannot be justified on the evidence presented.

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Evidence Against Rapid Emergence of Praziquantel Resistance in *Schistosoma haematobium*, Kenya–Reply to Drs. Coles, Liang, and Doenhoff

To the Editor: Drs. Coles, Liang, and Doenhoff have raised important issues regarding the emergence of praziquantel resistance in human populations. We agree that praziquantel resistance will undoubtedly emerge. In our recent modeling paper (1), we attempted to address the question of how soon such resistance will become clinically significant.

As Dr. Cole and colleagues discuss, in the future the best means for detecting resistance will be through laboratory testing of field isolates for resistance genes. In the meantime, in the absence of validated laboratory testing, analysis of ongoing clinical experience provides *Schistosoma haematobium* control programs some useful insight into the potential emergence of drug resistance.

Our modeling analysis of the emergence of praziquantel resistance took as its base-case the 8-year experience with treatment outcomes in an area of Kenya that had not previously been exposed to praziquantel. It was not, in fact, "a relatively small part of the population" that was treated, but rather the greater majority (75%-95% per year) of all school-aged children in the Msambweni area. Based on the uneven age distribution of *S. haematobium* infection (2), we estimated that 50%-75% of worms in the community were exposed to the drug during the treatment period. Sensitivity analysis allowed our model to address the implications of greater or lesser worm exposure and of greater or lesser prevalence of resistance genes.

Clearly, untreated worms in refugia would have played an important role in delaying emergence of resistance during the study period; our analysis suggests that attempts to increase community treatment coverage to 100% would have accelerated the emergence of clinically significant resistance. Similarly, a higher initial prevalence of resistance gene(s) or a faster genetic mutation rate would be predicted to hasten the onset of substantial levels of resistance. Still, on the basis of known features of parasite transmission dynamics, the effects of obligate sexual parasite reproduction and of worm clustering within human hosts were predicted to slow the emergence of resistance (on a population basis) by several years. We agree that Dr. Van Wyk's recent review on "Refugia" (3) provides a thought-provoking discussion of the effects of mass treatment of helminthic infections in a setting where drugs are not 100% effective in eradicating infection, where transmission quickly resumes, and where reinfection with resistant parasites is favored.

The title of our paper was not meant to cast doubt on the likelihood of praziquantel resistance. Instead, it was meant to point out that, under the conditions of our study, we observed no substantial praziquantel resistance and its emergence was not as "rapid" as might have been predicted. We concur that the spread of resistance will be accelerated

by widespread drug usage, and we emphasize that targeted treatment has the potential advantage of prolonging the useful lifespan of a drug such as praziquantel.

The conclusion of our modeling analysis is that there may be only a 7- to 10-year period during which control projects will consistent, drug-mediated reductions in worm burden. It is essential, therefore, that planners anticipate eventual drug failure and incorporate, as part of an integrated infection-management system, nondrug interventions that will prolong drug usefulness. Prevention of transmission and not just development of newer drugs will finally provide the best form of "therapy."

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