Are poor responses to praziquantel for the treatment of Schistosoma mansoni infections in Senegal due to resistance? An overview of the evidence

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Summary This paper summarizes and concludes in-depth field investigations on suspected resistance of Schistosoma mansoni to praziquantel in northern Senegal. Praziquantel at 40 mg/kg usually cures 70–90% of S. mansoni infections. In an initial trial in an epidemic S. mansoni focus in northern Senegal, only 18% of the cases became parasitologically negative 12 weeks after treatment, although the reduction in mean egg counts was within normal ranges (86%). Among other hypotheses to explain the observed low cure rate in this focus, the possibility of drug resistance or tolerance had to be considered. Subsequent field trials with a shorter follow-up period (6–8 weeks) yielded cure rates of 31–36%. Increasing the dose to 2 × 30 mg/kg did not significantly improve cure rates, whereas treatment with oxamniquine at 20 mg/kg resulted in a normal cure rate of 79%. The efficacy of praziquantel in this focus could be related to age and pre-treatment intensity but not to other host factors, including immune profiles and water contact patterns. Treatment with praziquantel of individuals from the area residing temporarily in an urban region with no transmission, and re-treatment after 3 weeks of non-cured individuals within the area resulted in normal cure rates (78–88%). The application of an epidemiological model taking into account the relation between egg counts and actual worm numbers indicated that the low cure rates in this Senegalese focus could be explained by assuming a 90% worm reduction after treatment with praziquantel; in average endemic situations, such a drug efficacy would result in normal cure rates. Laboratory studies by others on the presence or absence of praziquantel resistance in Senegalese schistosome strains have so far been inconclusive. We conclude that there is no convincing evidence for praziquantel-resistant S. mansoni in Senegal, and that the low cure rates can be attributed to high initial worm loads and intense transmission in this area.

keywords praziquantel, Schistosoma mansoni, drug resistance, low cure rates, Senegal, field data, modelling, review

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Introduction In the late 1980s, a massive outbreak of schistosomiasis mansoni occurred in the Senegal river basin (SRB) after the construction of a dam and subsequent water resource development (Talla et al. 1990, 1992; Gryseels et al. 1994; Vercruysse et al. 1994). In 1991, an unusually low cure rate of 18% was reported from the area after treatment with a standard dosage of praziquantel of 40 mg/kg. Heavy initial infections, intense transmission, and immunological naivety were assumed possible explanations, but emergence of a praziquantel-resistant or tolerant parasite strain had to be considered as well. The mere suggestion caused considerable commotion in the scientific community.
(WHO 1992, 1993a), as praziquantel is the cornerstone of current schistosomiasis control strategies (WHO 1983, 1985, 1993b). This paper summarizes the results of a systematic series of field studies which have since then been conducted to further investigate the efficacy of praziquantel, and the possible occurrence of drug resistance, in this Senegalese focus.

**First field report**

In 1991, we started to investigate the community of Ndombo (approximately 4000 inhabitants), situated 4 km south of Richard Toll, along the canal that links the Senegal river to the inland Lac de Guiers (Gryseels et al. 1994).

In the first, randomly selected study group, 91% of the people were infected, with 41% excreting more than 1000 eggs per gram of stool (epg) (Stelma et al. 1993). After standard treatment with praziquantel, the cure rate 12 weeks after treatment was only 18% (Stelma et al. 1995). The intensity reduction rate, on the other hand, was within normal ranges (86%). Antigen detection confirmed these results: only 10% of the individuals became negative in the serum circulating anodic antigen (CAA) enzyme-linked immunosorbent assay (ELISA) at 10 days and 12 weeks after treatment, although antigen levels decreased sharply. Side-effects were marked but transient (Stelma et al. 1995).

Population treatment of *Schistosoma mansoni* infections with praziquantel at a dose of 40 mg/kg usually results in parasitological cure rates of 70–90%, and egg count reduction rates of more than 90% (Gryseels et al. 1987; Davis 1993; WHO 1993b; Kumar & Gryseels 1994). Cure rates as low as observed in this focus had never been reported before, not even in foci with comparable endemicity (e.g. Homeida et al. 1988; Polderman et al. 1988).

**Further evidence**

Between January 1992 and September 1993, we examined, treated and followed-up another three randomly selected cohorts of approximately 400 subjects each, with 8-month intervals between each of the (in total) four groups (Gryseels et al. 1994). Each cohort was examined parasitologically (faecal egg counts), serologically (circulating antigen and antibody profiles), and clinically. Those found positive after parasitological examination (i.e. two stool examinations, each consisting of duplicate 25-mg Kato examinations) were treated with 40 mg/kg praziquantel in a single oral dose. These groups were followed up at 6 (rather than 12 in the first cohort) weeks after treatment.

As in the first study group, high prevalences and intensities of infection were observed in the three subsequent ones. Parasitological cure rates after treatment remained low (31–36%), while egg count reduction rates were between 83 and 90% (see Table 1).

We compared the efficacy of the standard dose of praziquantel with that of a higher, split dosage of praziquantel (2 × 30 mg/kg), such as recommended for intense infections by Davis (1993). One hundred and thirty heavily infected children from Ndombo were randomly allocated to the different treatment groups, and examined both by stool examination and CAA detection, before and at different time points after chemotherapy. The higher dosage resulted in slightly better, but not significantly different, cure rates (44% vs. 34% at 6 weeks after treatment). Mean egg counts were reduced by 99% in both groups. Antigen detection confirmed the parasitological results (Guissé et al. 1997; Table 1).

We went on to compare praziquantel with oxamniquine, the only available alternative and still highly effective drug for *S. mansoni*, to which no resistance has been described so far in Africa (Gryseels et al. 1987; Davis 1993). This comparative trial was conducted with a group of 138 people (5–75 years old) from the same focus of Ndombo (Stelma et al. 1997). Six weeks after treatment, parasitological cure rates with praziquantel at 40 mg/kg were again very low (36%), whereas treatment with oxamniquine at 20 mg/kg resulted in a cure rate of 79%, similar to those reported elsewhere (Gryseels et al. 1987; Tadese & Zein 1988). The reduction in egg counts was within normal ranges in both groups, but slightly lower in the praziquantel group than in the oxamniquine group (see Table 1).

**Possible explanations**

Several hypotheses were explored to explain the various results with praziquantel in this focus. Before testing other hypotheses, the possibility of poor drug quality was checked. The used batch of praziquantel was shown to be normally effective in a mouse model (Stelma et al. 1995). Also, tablets were swallowed under supervision, and people who vomited soon after treatment were not included in the analyses. Poor bioavailability due to genetic or dietary factors could not be studied in this non-clinical setting.

**Diagnostic factors**

A substantial proportion of (light) *S. mansoni* infections can be missed with the Kato–Katz method (De Vlas & Gryseels 1992). Repeated egg counts in consecutive samples improve the sensitivity, and thus also affect the calculated cure rates. In most praziquantel field studies, cure rates have been determined on the basis of one or two Kato slides from only one stool sample (e.g. Polderman et al. 1988; Simonsen...
et al. 1990; Picquet et al. 1998). In Senegal, two to three stool samples were examined (Table 1). For comparison and reference, we recalculated the cure rates in the four Ndombo cohorts on the basis of only one stool egg count. As shown in Table 2, cure rates were considerably higher, but still lower than in other studies.

### Epidemiological factors

The very high egg counts in Ndombo raised the obvious hypothesis that, even if the drug was 99% effective, many people would still harbour a sufficient number of surviving schistosomes to account for light but discernible post-treatment egg excretion (Stelma et al. 1995). Our antigen detection results after treatment confirmed that in most patients adult worms did persist after treatment (Stelma et al. 1995). Although cure rates were associated with pre-treatment egg counts, low cure rates were not limited to heavily infected individuals, however (Stelma et al. 1995; Van Lieshout et al. 1999). Moreover, in an equally heavily infected population in Maniema (Congo), considerably higher cure rates had been found, albeit with a less sensitive diagnostic method (Polderman et al. 1988).

Given the obviously intense transmission in this area, many individuals might have carried pre-patent infections at the time of treatment. As immature schistosomes are largely insensitive to praziquantel (Xiao et al. 1985), this could also explain why egg excretion persisted in so many individuals after treatment. In the first trial, the low cure rates could also have been the result of rapid re-infection; indeed, cure rates improved when the follow-up period was shortened from 12 (cohort 1) to 6 weeks (cohort 2–4) although not to a ‘normal’ level.

### Host-related factors

In mice, adequate immune responses are a prerequisite for full efficacy of praziquantel (Brindley & Sher 1987), but it
is unclear whether these findings can be extrapolated to humans. We considered the possibility that in this very recent Senegal focus, immune mechanisms were not yet sufficiently developed at the time of treatment. First of all, drug efficacy remained equally low in four cohorts treated over a 2-year period, in which one might have expected further immune maturation of the population. We also found no association between levels of specific antibodies against adult worm antigen (AWA) and failure of praziquantel treatment, and no consistent linear trend in antibody levels across the four cohorts (Van Lieshout et al. 1999).

Other host-related factors, including sex, history of exposure, previous praziquantel treatment, and individual water contact behaviour could not be related to the efficacy of praziquantel either (Van Lieshout et al. 1999). The only host-related factors associated with low cure rates were age and pre-treatment egg counts: cure rates were significantly lower in the highest egg count groups, and, after allowing for intensity of infection, in children than in adults.

Drug resistance

Drug resistance in helminths is well known in animal nematodes, and has been described for schistosomes to hycanthone and oxamnique (Cioli et al. 1993; Geerts & Gryseels 2000). The danger of inducing praziquantel resistance, particularly in populations under strong selective pressure by large-scale chemotherapy, is therefore not negligible (Cioli et al. 1993). In laboratory settings, it appears surprisingly easy to select resistant strains under drug pressure (Fallon & Doenhoff 1994). In countries like Egypt, where school children and other target groups are treated twice annually, a specific resistance monitoring system has therefore been set up (El Khoby et al. 1998). In Senegal, praziquantel had been used quite extensively at the onset of the outbreak, often at suboptimal doses of 30 mg/kg (Kongs et al. 1994). Moreover, the parasite population in this area may be ‘clonal’; it was probably introduced by one or some immigrants and spread explosively into the dense and closely interacting snail and human populations (Gryseels et al. 1994). If this initially introduced strain, possibly further selected by treatment, was at the low end of the natural susceptibility range, generalized tolerance would not be such an unlikely scenario. Unfortunately, knowledge of the schistosome genome at that time, let alone its variation and possible markers for praziquantel resistance, did not allow to investigate this hypothesis genetically.

The ‘normal’ cure rates with oxamnique appeared to support the hypothesis of reduced praziquantel suscepti-

bility of the local schistosome strain. However, they may also be (partly) explained by a slightly stronger inherent schistosomicidal effect of oxamnique as compared with praziquantel (Geerts & Gryseels 2000). Moreover, oxamnique has a different working mechanism than praziquantel, e.g. the action of oxamnique does not, or at least not in the same way, depend on immune responses as does the one of praziquantel. It may thus be that, under the specific conditions in Senegal, oxamnique would indeed be a more efficacious drug than praziquantel (Stelma et al. 1997; Cioli 2000).

Laboratory studies

Other groups have independently conducted experimental studies to investigate the in vivo and in vitro susceptibility of the Senegalese schistosome strains to praziquantel. Fallon et al. (1995) found an S. mansoni isolate, obtained from snails collected in the Richard Toll area, to be unsusceptible to praziquantel when treated in mice. These findings were in fact contradictory to the observed high egg count reduction rates in humans. Praziquantel was administered to the mice at 35–37 days after infection, when a large proportion of schistosomes may still be immature and thus insensitive to the drug (Sabah et al. 1986). This left the possibility that the Senegalese isolate could be slow in reaching maturation and thus drug sensitivity. An experiment in which praziquantel was administered at 60 days after infection indeed showed a markedly improved efficacy, although still lower than in other geographical strains (Fallon et al. 1997).

In another laboratory, worm isolates derived from snails naturally infected in the Richard Toll area and six isolates derived from uncured Senegalese patients treated up to three times with praziquantel were tested in vitro and in vivo. No clear evidence was found for reduced susceptibility of any of the isolates to praziquantel (L. Pica-Mattoccia & D. Cioli, unpublished results). However, only single drug doses were tested, which is a rather insensitive approach to detect small differences between sensitive and resistant worms. Optimally, to detect a modest level of insensitivity to praziquantel, several drug doses should have been administered, and the ED50 values determined (Pica-Mattoccia & Cioli, personal communication).

Laboratory tests have, in our view, so far not provided convincing evidence for the presence (or absence) of a praziquantel resistant schistosome strain in Senegal. Resistant parasite strains would have been isolated from non-responding patients in one area in Egypt, but again the evidence was not conclusive (Ismail et al. 1996, 1999; Bennett et al. 1997). Generally, a lack of standardized methods and reference material hamper in vivo and
certainly in vitro detection of resistance in human helminths (Geerts & Gryseels 2000).

**Modelling**

Using a stochastic Monte Carlo simulation model relating egg counts to actual worm pair loads, the relationship of praziquantel efficacy with prevalence, geometrical mean, cure rates and intensity reduction was predicted for the situation in Ndombo (see Appendix). In this way, we could mathematically check the hypothesis that high pre-treatment parasite loads combined with the inherent diagnostic limitations of faecal egg counts could explain the observed data.

Figure 1a shows that cure rates rise with the mean efficacy of the drug. The efficacy is defined as the percentage worm pair reduction and assumed to vary between individuals. With a coefficient of variation (CV) = 0, cure rates remained very low (below 40%), even if almost 99% of the worms were removed by treatment. Apparently, initial worm burdens – in this exceptional case estimated to average more than 5000 per individual (see Appendix) – were high enough to leave most treated individuals with a sufficient number of worm pairs to remain positive at follow-up. Higher individual variation (CV > 0.0) yielded higher cure rates, as relatively more individuals would be completely cured.

Intensity reductions (i.e. geometrical mean egg counts among positive cases before and after treatment) show much higher values than cure rates. Model predictions matched the assumed efficacy of the drug (Figure 1b). For a mean praziquantel efficacy below 95%, individual variation did not markedly influence intensity reduction. For higher values of praziquantel efficacy, predictions of intensity reduction are less accurate as only some individuals with positive egg counts (on which the geometrical mean egg counts are based) remain after treatment. As shown in Figure 1b, intensity reduction decreases with higher efficacy, especially in combination with higher individual variation (CV > 0.1) because individual worm burden reduction will then be close to either 100 or 0%. As only the latter category determines the intensity reduction, mean egg counts after treatment will thus not differ much from those before treatment (i.e. intensity reduction approximates zero).

Figure 1 shows that a combination of mean efficacy = 90% and CV = 0.05 corresponds with the observed cure rate and intensity reduction in cohort 1. An average worm pair reduction of 90% does not indicate a poor drug performance, on the contrary. Assuming such an efficacy for average endemic situations (prevalence 40%, mean 100 epg) resulted in normal cure rates of 70–80% (not shown).

For cohort 4, drug efficacy was comparable (89%). Fitting the model to a data set from a typical moderate
endemic situation in Burundi (prevalence 40%, mean 113 epg, cure rate 83%, intensity reduction 56%; Gryseels et al. 1987) resulted in a slightly higher drug efficacy of 94% (data not shown). The efficacy of praziquantel in Ndombo seems thus of the same order of magnitude as the values estimated for endemic situations where initial intensities of infection were lower.

Further field studies

To further investigate the role of factors related to intense transmission, we conducted two field studies in which the influence of these factors was eliminated or minimized. The first field study was based on the concept of two closely spaced courses of treatment to eliminate most parasites having survived the first treatment, proposed by an European Commission (EC)-sponsored praziquantel network (Renganathan & Cioli 1998). In the high transmission village of Ndombo, a group of 145 children and adolescents (9–25 years) who had never been treated before were treated twice with praziquantel 40 mg/kg, at an interval of 3 weeks. Stool examinations (duplicate 25 mg Kato–Katz slides from two different stools) were performed immediately before the first treatment, and 5 weeks afterwards. After both treatments, the cure rate observed in this group was 88% and the egg reduction rate 91% (Table 1). Similar results were observed by Picquet et al. (1998) in an independent study in Nder, a village 25 km south of Ndombo. One other study with repeated treatments in the village of Ndombo however, yielded less satisfactory results (Tchuem-Tchuente´ et al. 2001). In both these studies interval and follow up time were relatively long compared with ours. Apparently, these episodes were too large to adequately eliminate all interfering factors.
because of the high transmission levels in Ndombo. In Nder, the influence of these factors may have been less as this study was conducted in the low transmission season (Tchuem-Tchuente et al. 2001).

In the second field study, praziquantel was evaluated in a group of 100 infected students (12–24 years) from the Richard Toll area, during their stay in a boarding school in St Louis, where no S. mansoni transmission occurs. The adolescents were treated with praziquantel 40 mg/kg, 3 weeks after arriving in the transmission-free area, in order to allow pre-patent infections to mature and become fully susceptible to the drug. Stool examinations (duplicate 25 mg Kato slides from two different stool samples) were performed immediately before treatment, and 3 and 6 weeks after treatment. The cure rate in this group at 3 weeks after administration of praziquantel was 93%, with an egg reduction rate of 80%. Six weeks after treatment these figures were 78 and 86%, respectively (Table 1). It should be noted however, that the mean intensity of infection in this group was lower than in the Ndombo focus.

Nevertheless, the results of these studies indicate that, when the influence of intense and continuous transmission is eliminated or minimized, the efficacy of praziquantel in human S. mansoni infection in this area comes within normal ranges.

Conclusions

The overall conclusion we draw from these studies is that there is no convincing evidence of resistance, tolerance or reduced susceptibility of S. mansoni to praziquantel in Senegal, and that the observed low cure rates are largely the result of the specific epidemiological situation. The low cure rates observed after a single treatment under continuous intense transmission can be explained by high initial worm loads, rapid re-infection, maturation of pre-patent infections, or a combination of these factors.

It also appears from these studies, however, that current tools, methods and reference material are inadequate or too laborious to detect problems of praziquantel tolerance or resistance in an early stage or at a low level (Geerts & Gryseels 2000). The applied model projects that in Ndombo praziquantel would have reduced worm burdens by 89–90%, and in a moderately endemic situation in Burundi by 94%. Apart from other possible methodological and biological explanations, such a small reduction of susceptibility could never be conclusively demonstrated with the current field and laboratory methods. In livestock helminths, it is estimated that resistance becomes epidemiologically detectable only when 25% of the worms have become resistant. At that level, it is too late for interventions to contain drug resistance (Geerts & Gryseels 2000).

Although there is as yet no immediate concern for praziquantel resistance in Senegal or elsewhere, we should remain alert. To avoid scenarios such as the dramatic spread of anthelmintic drug resistance in livestock, appropriate methods and strategies for a reliable and early detection and surveillance of resistance must urgently be developed. Also, alternative drugs such as oxamniquine should be kept readily available, and research and development of new anti-schistosomal drugs actively pursued (Cioli 1998, 2000; Geerts & Gryseels 2000).

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Appendix

The model: linking cure rate and intensity reduction rate to efficacy of the drug

The aim of the model is to translate observations in terms of observed Schistosoma mansoni egg counts (prevalence, geometrical mean, cure rate and intensity reduction) to underlying processes at the worm or worm pair level. The model can be considered an extension of earlier modelling work to relate repeated individual S. mansoni egg counts to population worm pair burdens (De Vlas et al. 1992).

The number of worms per individual n is assumed to follow a negative binomial distribution with mean worm burden M and aggregation parameter k. The smaller the value of k, the more the worms are concentrated in a small, highly infected part of the population. High values of k mean that all individuals have about the same chance of being infected, approximating a Poisson distribution. The worm pair distribution is the result of applying a mating process to the distribution of worms. If \( n_{\text{fem}} \) represents the number of female worms, and thus \( n = n_{\text{fem}} \) the number of male worms, then \( x = \min(n_{\text{fem}}, n - n_{\text{fem}}) \) is considered the number of worm pairs in case of monogamous mating; \( n_{\text{fem}} \) follows from a binomial distribution with parameters \( n \) and 0.5, assuming a ratio of male to female worms of 1:1. The faecal egg count \( y \) for a given number of worm pairs is assumed to follow a negative binomial distribution with the mean egg count being a proportional function \( b \cdot x \) of the number of worm pairs \( x \), and aggregation parameter \( r \). The values of \( b \) and \( r \) depend on the amount of stool investigated: here, duplicate 25 mg Kato slides examined on two subsequent days. From extensive previous fitting procedures, their values have been estimated at \( b = 0.10 \) and \( r = 1.98 \) to represent such a situation (De Vlas 1996).

Using only \( M \) and \( k \) as free parameters, this model has proven to be suitable to fit population egg counts of S. mansoni infection in any endemic situation. Moreover, it has been shown that the observed prevalence and geometrical mean egg count among positives are sufficient population measures to determine \( M \) and \( k \), and to make further inferences. For example, a pocket chart to predict true prevalences from observed prevalence and geometrical mean has been developed and validated using this principle (De Vlas et al. 1993, 1997). For the initial trial in Ndombo (cohort 1), a pre-treatment prevalence of 90% and a geometrical mean of 700 epg correspond to values of \( M = 5200 \) and \( k = 0.41 \).

For the current study, the model was extended by including the effect of praziquantel (PZQ) as a reduction in the number of worm pairs \( (x_{\text{pre}} \text{ vs. } x_{\text{post}}) \). This effect is (1) the killing of worms, and possibly, (2) immature worms developing into egg laying adults, and (3) re-infection (see main text). The model does not distinguish among the three phenomena but considers them in combination. The number of worm pairs post-treatment \( x_{\text{post}} \) is assumed to follow from a binomial distribution with parameters \( x_{\text{pre}} \) and PZQ efficacy ‘\( e \)’. The value of ‘\( e \)’ is supposed to vary between individuals (ranging from a proportion of 0.0–1.0 worm pair reduction) according to a Beta distribution with shape parameters \( a_1 > 0 \) and \( a_2 > 0 \) (Law & Kelton 1991). It can be shown that \( a_1 \) and \( a_2 \) correspond to a unique combination of the mean efficacy (mean) and coefficient of variation (CV) = \( \sqrt{\text{variance}/\text{mean}} \) by \( a_1 = (1.0 - \text{mean})/\text{CV}^2 - \text{mean} \) and \( a_2 = a_1/\text{mean} - a_1 \).

In the analyses, we have chosen mean and CV to represent the efficacy of the drug. Similar to the pre-treatment situation, the egg count \( y_{\text{post}} \) after treatment is assumed to follow a negative binomial with the mean egg count being a proportional function \( b \cdot x_{\text{post}} \) of the number...
of worm pairs $x_{\text{post}}$, and aggregation parameter $r$. The values of $h$ and $r$ are the same as pre-treatment.

For the pre-set values of $M$, $k$, $h$ and $r$ and various combinations of mean PZQ efficacy and CV, predictions of cure rate and geometrical mean intensity reduction have been made by Monte Carlo simulation of a series of 100 000 individuals (Law & Kelton 1991). For each individual, random samples of the initial worm load, number of female worms (and resulting pre-treatment worm pair load), the efficacy of the drug, the worm pair load after treatment, and the corresponding egg counts before and after treatment were obtained (see Figure 2). The combination of assumed mean efficacy and CV which matches the observed cure rate and intensity reduction provides insight into the effect of the drug at the worm level.