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Increase of intestinal schistosomiasis after praziquantel treatment in a *Schistosoma haematobium* and *Schistosoma mansoni* mixed focus

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Abstract

The recent emergence of a mixed focus of *Schistosoma haematobium–Schistosoma mansoni*, in the lower delta of the Senegal river, requires adapted control programmes. A mass treatment with praziquantel was organised in April 1994 by local authorities in three villages where populations had been examined. A total of 2042 subjects participated. In Savoigne *S. haematobium* prevailed (53% for prevalence), in Diagambaly *S. haematobium* (64%) and *S. mansoni* (76%) were both abundant, and in Boundoum *S. mansoni* prevailed (53%). Therapeutic coverage (80%) was assessed on a representative sample. A cohort of 968 treated subjects were followed-up 40, 100, 200 and 300 days after treatment. Six weeks after treatment, the average of egg excretion decreased by 95% for *S. haematobium*, ranging from 23 to one egg(s)/10 ml at Savoigne and from 14 to one egg(s)/10 ml at Diagambal. Conversely, egg excretion only decreased by 75% for *S. mansoni*, from 23 to six eggs/g at Boundoum and from 69 to 16 eggs/g at Diagambal, showing evidence of the low susceptibility of *S. mansoni* local strain to praziquantel. Ten months after treatment, reinfections with *S. haematobium* remained weak at Savoigne (two eggs/10 ml) while those with *S. mansoni*

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were so high at Boundoum (24 eggs/g) that they compensated the reduction of load induced by the treatment. At Diagambal, where the two parasites were present before treatment, the disappearance of the urinary schistosomiasis after treatment concurred with a dramatic increase of intestinal schistosomiasis. *S. mansoni* egg excretion was seven times higher than before treatment (478 eggs/g). These different effects of treatment are discussed according to the ecology of transmission in the three villages.

Keywords: *Schistosoma mansoni*; *Schistosoma haematobium*; Mass treatment; Praziquantel; Reinfections; Senegal

1. Introduction

Following the period of drought, during the 1970s, the Senegal river valley was harnessed to control the flow of the river and to further agricultural development. Since 1986, the dam of Diama (Senegal), 20 km near the mouth, protects the delta from salt water intrusion during dry periods. Since 1988, the dam of Manantali (Mali) located on the river Bafing, the main tributary of Senegal river, permits regulation of the flow of the river. The extended flood period resulted in the development of snail populations, including intermediate hosts of human schistosomiasis.

Prior to the construction of the dams, urinary schistosomiasis was endemic in the valley of Senegal. The transmission involved *Bulinus senegalensis* except for an isolated focus in the lower delta where the intermediate host was *Bulinus globosus*. This area of the delta benefited from a more regular water supply and was protected from salt water intrusions, offering favourable conditions for the development of this snail (Vercruysse et al., 1985).

After building the dams, the epidemiological situation rapidly evolved: emergence of an important urban focus of intestinal schistosomiasis was observed at Richard Toll (Talla et al., 1990) and the urinary schistosomiasis focus of lower delta spread towards upstream (Verlé et al., 1994). These changes were explained by the role of the dams on the development of the intermediate hosts *Biomphalaria pfeifferi* and *Bulinus globosus* (Vercruysse et al., 1994). Several surveys were performed in January 1994 (Picquet et al., 1996) and showed an extension of the distribution area of *Schistosoma mansoni* with a possibility of partial overlapping with *Schistosoma haematobium*. This created an *S. haematobium–S. mansoni* mixed focus in the lower delta, with *S. haematobium* prevailing in the upstream part and *S. haematobium* prevailing in the downstream part.

The aim of the present study was to estimate the efficiency of a mass treatment with praziquantel in this *S. haematobium–S. mansoni* mixed focus of the delta of the Senegal river.

2. Materials and methods

2.1. Villages

In January 1994, a cluster sample survey (Picquet et al., 1996) selected three villages located in the extension zone of schistosomiasis: Savoigne where *S. haematobium* prevailed, Diagambal where *S. haematobium* and *S. mansoni* were both abundant, and Boundoum where *S. mansoni* prevailed. Dispensaries were present at Savoigne and Boundoum, whereas Diagambal only benefited from primary health care. These health care resources were mainly used and the use of praziquantel was rare. An exhaustive census of the resident population (cumulated absence inferior to 2 months during the previous year) was carried out in each village studied (Table 1). Parasite examinations were carried out on all subjects above 4 years old. A total of 2042 persons had a full examination, including two stool samples and one urine sample. For stools, duplicate 25 mg Kato–Katz thick smears were prepared and eggs were counted at two day intervals. Ten millilitres of urine were collected between 11:00 h and 15:00 h and filtered through Nytrel 20. The eggs were then counted after iodine staining.

2.2. Treatment

At the end of April 1994, within the framework of a mass treatment organised by the health authorities, treatment with praziquantel was proposed to the whole population of the three villages studied. The treatment (40 mg/kg) was administered the same day under medical supervision. Women in the three first months of pregnancy or breast-feeding children under 6 weeks, children under 5 years old and subjects who received praziquantel within the two previous months were excluded from the treatment. No other treatment was realised during the following year.

Table 1
General characteristics of the three study populations

Village	Savoigne	Diagambal	Boundoum
Residents	821	603	1538
Examined people (stools+urine)	625	450	967
Prevalence of *S. haematobium* (urine)	53.3 % ± 3.9	64.4% ± 4.4	1.2% ± 0.7
Geometric mean load (eggs/10 ml)	9.7 (7.6; 12.2)	10.6 (8.4; 13.4)	0.04 (0.0; 0.1)
Prevalence of *S. mansoni* (stools)	8.0% ± 2.1	75.6% ± 4.0	53.1% ± 3.1
Geometric mean load (eggs/g)	0.4 (0.3; 0.5)	66.4 (51.6; 85.3)	14.5 (12.0; 17.5)
Sample fort therapeutic assessment	425	450	331
Therapeutic coverage	86.8% ± 3.2	73.8% ± 4.1	80.7% ± 4.3
Cohort	369	332	267

2.3. Therapeutic assessment

Therapeutic coverage was assessed on a representative sample of the examined population (1410 persons). These subjects were issued respectively from the population of the main quarter at Savoigne (506 persons), from the whole population at Diagambal (500 persons), and from a random sample of families at Boundoum (404 persons). Because a list of treated people was not available, the therapeutic coverage was evaluated after individual query (dosing and dosage) during week following treatment. Only the subjects who gave a concordant reply were considered as treated. Parasite controls were proposed to these 968 treated subjects on 40, 100, 200 and 300 days after treatment. Parasite investigations were unchanged during the investigation.

2.4. Data analysis

Only persons who gave both urine and stools were included in analysis. Prevalence and geometric mean of egg excretion (Williams' geometric mean (WGM)) were compared using bilateral χ^2 and Student's t-test. $P < 0.05$ was considered as significant in these analyses.

3. Results

3.1. Parasite evaluation before treatment

Prevalence of *S. haematobium* was high at Savoigne (53%) and at Diagambal (64%) (Table 1). The average egg excretion was similar in these two villages (11 and 10 eggs/10 ml, respectively) and decreased with age. One of the two quarters of Savoigne seemed to bear more infection and therapeutic assessment has concerned its population. At Boundoum, this parasite was practically absent (1% and 0.1 egg/10 ml).

Prevalence of *S. mansoni* was high at Diagambal (76%) and at Boundoum (53%) (Table 1). The average egg excretion was higher ($P < 0.001$) at Diagambal (66 eggs/g) than at Boundoum (15 eggs/g) ($P < 0.001$) and decreased slowly with age. Intestinal schistosomiasis was of lesser importance at Savoigne (8% and 0.4 egg/g).

3.2. Effect of treatment on S. haematobium loads

From D0 to D40 after distribution of praziquantel, the prevalence of *S. haematobium* decreased dramatically in cohorts of Savoigne (from 64 to 12%) and Diagambal (from 66 to 26%) ($P < 0.001$) (Fig. 1). The important decrease in egg excretion in the two villages (reduction rate of 98 and 91%) confirmed the effectiveness of praziquantel on *S. haematobium*.

At Savoigne (Fig. 1), the prevalence increased slightly from D40 to D100 (end of dry season), but remained stable from D100 to D200 (rainy season). The prevalence

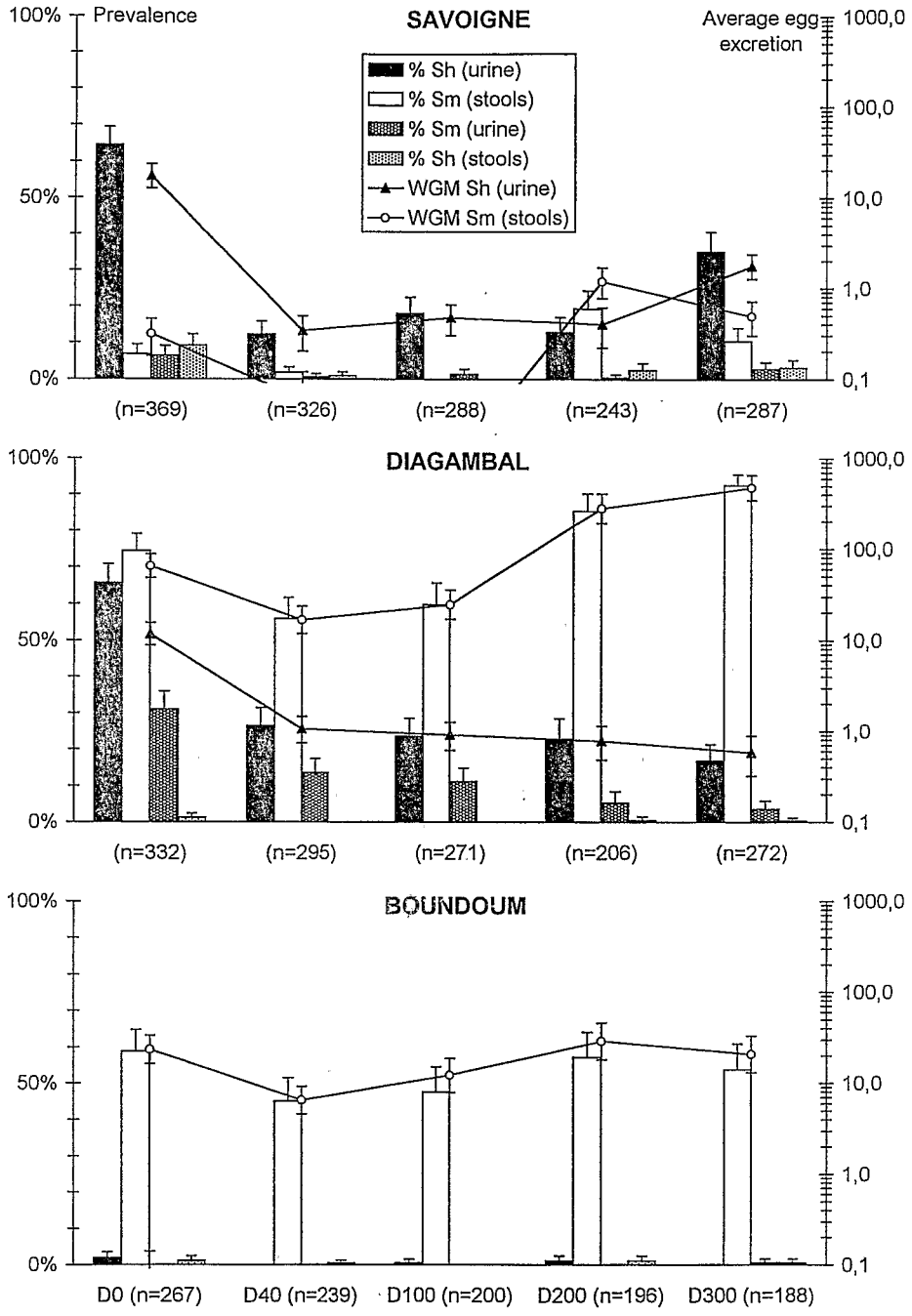

Fig. 1. Effect of treatment with praziquantel on the prevalence and the average egg excretion (WGM) of *S. haematobium* and *S. mansoni* in human populations from three villages of the delta of the Senegal River (Senegal).

raised to 35% ($P < 0.001$) from D200 to D300 (cold dry season). The average egg excretion followed a similar pattern but remained clearly above the value observed before treatment (two and 17 eggs/10 ml, $P < 0.001$). Conversely, at Diagambal (Fig. 1), prevalence and egg excretion of *S. haematobium* kept decreasing during the survey. At Boundoum (Fig. 1), urinary schistosomiasis remained absent.

3.3. Effect of treatment on S. mansoni loads

From D0 to D40 after treatment, the prevalence of *S. mansoni* had reduced only lightly at Diagambal (Fig. 1), respectively from 74 to 56% ($P < 0.001$) and from 59 to 45% ($P < 0.01$). This reduction was lower for children and the average egg excretion remained high (20 and 49 eggs/10 ml, respectively).

At Boundoum (Fig. 1), the prevalence increased from D100 to D200 (rainy season) ($P < 0.01$) reaching its pretreatment value (57%). Concurrently the average egg excretion increased from D40 to D200 ($P < 0.001$), reaching its initial value (57 eggs/10 ml). For children, these values were higher than before treatment: the prevalence increased from 70 to 78% and the average egg excretion raised from 58 to 108 eggs/g.

At Diagambal (Fig. 1), this increase was more abrupt. From D100 to D200, the prevalence raised from 60 to 85% ($P < 0.01$) and the average egg excretion raised from 25 to 281 eggs/g ($P < 0.001$), exceeding the values before treatment. This increase continued after the rainy season and at D300, 93% of the population excreted eggs in stools and their average egg excretion reached 478 eggs/g (1088 eggs/g for children).

Paradoxically, as before treatment, the presence of *S. mansoni* eggs in urine was observed in 31% of the subjects, this observation became scarce after treatment. In spite of the considerable increase of intestinal schistosomiasis, the prevalence of *S. mansoni* eggs in urine decreased concurrently to the prevalence of urinary schistosomiasis.

At Savoigne (Fig. 1), prevalence of *S. mansoni* raised on D200 (35%) but the intensity of excretion remained very weak. These values decreased from D200 to D300 (cold dry season). Excretion of *mansoni* eggs in urine was also observed before treatment (7%) and reappeared 10 months later (3%) as the prevalence of *S. haematobium* increased.

4. Discussion

4.1. Parasite situation before treatment

Investigations of the three villages of Savoigne, Diagambal and Boundoum confirmed the recent extension of intestinal schistosomiasis focus that emerged at Richard Toll (Talla et al., 1990). This focus has been spreading along the river from upstream to downstream but has not yet reached the downstream part of the delta. Savoigne was in an intermediate situation with a still weak presence of *S. mansoni*.

Since the first observations of Verlé et al. (1994), the *S. haematobium* focus of lower delta has extended slowly upstream.

4.2. Effect of treatment on S. haematobium loads

In villages endemic for *S. haematobium*, the average egg excretion in urine was reduced by more than 90% 6 weeks after treatment with praziquantel, confirming the effectiveness of this drug on *S. haematobium* (Sellin et al., 1986). In spite of reinfections observed during the cold dry season, parasite indices remained clearly reduced 10 months after treatment, including in children, and chemotherapy appeared sufficient to control the disease.

4.3. Effect of treatment on S. mansoni loads

The effectiveness of praziquantel on *S. mansoni* was notably poor at Diagambal and Boundoum. Six weeks after treatment, the average intestinal egg excretion was 25% of its initial value and 60% of the infected subjects continued to excrete eggs in their stools. This poor result, which is clearly inferior to the normal activity of the drug on *S. mansoni* (Kumar and Gryseels, 1994), appeared to be a characteristic of the focus of the delta of Senegal (Stelma et al., 1995). The hypothesis of early re-infections has to be rejected due to the 6-weeks observation. This period is too short for the development of adult worms. Similarly, because transmission of *S. mansoni* was not observed during the 2 months prior to treatment (Ernould et al., 1999), it is unlikely that immature stages, known to be less sensitive to praziquantel (Shaw, 1990), were present at the time of the treatment.

The fact that this focus was recent could have contributed to a weaker therapeutic response since it has been demonstrated that the specific immune response developed by the host acted synergistically with praziquantel action on *S. mansoni* (Doenhoff, 1989). In case of partial specific immune response, a lower effect of praziquantel should be expected. However, immuno-epidemiologic studies performed near Richard Toll revealed the major role of age as compared to the exposure time for the development of the immune response (Van Dam et al., 1996). It was therefore not possible to explain the weakness of the therapeutic response in adults by the newness of this focus. These results could be related to the expression of a partial resistance to praziquantel by the delta population of *S. mansoni* (Stelma et al., 1995) as shown by experimental studies (Fallon et al., 1995).

At Boundoum, parasite indices remained stable during the dry season, a period where *S. mansoni* transmission seemed very low. In contrast, they increased quickly during the rainy season and their values became as high as they were before treatment. This increase in egg excretion should be attributed to new acquired infections rather than an hypothetical compensating hyperactivity of worms which survived treatment (Medley and Anderson, 1985), that should have been observed at the second control. If *S. mansoni* transmission appeared very high during the rainy season, it occurred only over a short period (Ernould et al., 1999). The loss of therapeutic benefit within a year confirmed the difficulty to control *S. mansoni*

infection by the only mean of chemotherapy in high transmission focus (Gryseels & Nkulikyinka, 1989).

At Diagambal, a village where both *S. haematobium* and *S. mansoni* were co-endemic, the situation was more alarming. Parasite indices raised significantly during the rainy season, exceeding pretreatment values. A total of 85% of subjects excreted *S. mansoni* eggs in stools and the intensity of excretion was three times superior to that before treatment. The increase continued after this transmission period, probably resulting from the maturation of new acquired worms. Ten months after treatment over 90% of subjects were infected and the average egg excretion was seven times higher than that prior to treatment, reaching nearly 500 eggs/g. This situation was particularly serious for children as they were all infected, with an average egg excretion exceeding 1000 eggs/g. In a similar epidemiological situation in Sudan, the rarity of reinfections with *S. haematobium* also contrasted with the high reinfections with *S. mansoni*. However, *S. mansoni* infections remained lower than before treatment (Kardaman et al., 1985).

The reduction of *S. mansoni* loads observed 6 weeks after treatment both in Boundoum and Diagambal allowed us to reject the hypothesis of a lesser activity of praziquantel on *S. mansoni* in case of co-infection with *S. haematobium*. Another hypothesis could be a competition between the two parasite populations within their common host at Diagambal. Indeed, we observed a surprisingly high prevalence (31%) of lateral spine egg excretion in urine before treatment. This mode of excretion is generally attributed to heterologous mating between male *S. haematobium* and female *S. mansoni* (Ratard et al., 1991). The fact that this observation became scarce with the progressive disappearance of *S. haematobium*, in spite of the increase of *S. mansoni* loads, seemed to support this hypothesis. According to a recent experimental work, this heterologous mating could express a sexual interspecific competition (Tchuem Tchuente et al., 1996). In the present case, this sexual interaction would result in a capture of females *S. mansoni* by males *S. haematobium*. The very high effectiveness of praziquantel on *S. haematobium* would have induced an eviction of this species, suppressing the sexual interaction and therefore helping the increase of *S. mansoni*, less sensitive to treatment.

However, the high prevalence of *S. mansoni* in the population of Diagambal before treatment, despite the high prevalence of *S. haematobium*, indicates that such a sexual interaction is not sufficient to limit *S. mansoni* development. The suppression of this interaction could therefore contribute to but not explain the increase of *S. mansoni* infection in this village.

Presence of *S. mansoni* at Diagambal is probably recent and our observations before treatment can reflect the parasite situation in a focus in progress. Treatment with praziquantel reduced only partially *S. mansoni* loads, and the transmission has been able to remain at a high level after treatment. Differences observed between Boundoum and Diagambal could be related to the more favourable transmission conditions in this later village (good accessibility and low speed of flow in transmission sites). This particular ecological situation would explain that in less than one year the parasite indices of *S. mansoni* at Diagambal became similar to those exceptionally high indices observed near Richard Toll (Stelma et al., 1993).

5. Conclusion

Mass treatment with praziquantel resulted in an efficient control of *S. haematobium* infection. Reinfections remained moderate ten months after treatment and affected mainly children, who therefore represent the main target for future control programmes. In contrast, mass treatment with praziquantel had only a short and partial effect on *S. mansoni* infection. The reduction in parasite load was weak, and transmission remains high, resulting in high level of reinfections during the following year. This situation was partially explained by the low susceptibility of this local strain to praziquantel. In addition, the very high intensity of transmission is not compatible with a control of schistosomiasis using mass treatment alone. These observations underline the need for alternative strategies combining for example chemotherapy and vaccine.

In a village where both *S. haematobium* and *S. mansoni* were endemic, the treatment resulted in a suppression of urinary schistosomiasis but a dramatic aggravation of intestinal schistosomiasis. The differential activity of praziquantel on the two parasites not only maintained a high *S. mansoni* load but may also have contributed to *S. mansoni* development by suppressing a possible sexual interaction with *S. haematobium*. These circumstances combined with particularly favourable transmission conditions resulted in a very high contamination level. These observations underline the need to select appropriate control strategies according to the schistosome species, their possible interactions as well as the ecology of transmission, both at the level of intermediate host and human populations.

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