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Regular treatments of praziquantel do not impact on the genetic make-up of *Schistosoma mansoni* in Northern Senegal

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ABSTRACT

The Senegal River Basin (SRB) experienced a major epidemic of intestinal schistosomiasis in the early nineties, after the construction of a dam for irrigation purposes. Exceptionally low cure rates following praziquantel (PZQ) treatment at the onset of the epidemic raised concerns about PZQ resistant strains of *Schistosoma mansoni*, although they could also be attributed to the intense transmission at that time. A field study in the same region more than 15 years later found cure rates for *S. mansoni* still to be low, whereas *Schistosomahaematobium* responded well to treatment. We collected *S. mansoni* miracidia from children at base-line prior to treatment, six months after two PZQ treatments and two years after the start of the study when they had received a total of five PZQ treatments. In total, 434 miracidia from 12 children were successfully genotyped with at least six out of nine DNA microsatellite loci. We found no significant differences in the genetic diversity of, and genetic differentiation between parasite populations before and after repeated treatment, suggesting that PZQ treatment does not have an impact on the neutral evolution of the parasite. This is in stark contrast with a similar study in Tanzania where a significant decrease in genetic diversity was observed in *S. mansoni* miracidia after a single round of PZQ treatment. We argue that PZQ resistance might play a role in our study area, although rapid re-infection cannot be excluded. It is important to monitor this situation carefully and conduct larger field studies with short-term follow-up after treatment. Since PZQ is the only general schistosomicide available, the possibility of PZQ resistance is of great concern both for disease control and for curative use in clinical practice.

1. Introduction

Schistosomiasis or bilharzia is a parasitic disease that mainly occurs in tropical and subtropical regions of the world and is caused by blood flukes of the genus *Schistosoma* (subclass Digenea); over 200 million people are infected, of which more than 90% live in Africa (Hotez and Kamath, 2009). *Schistosoma* species have a two-host life cycle with an asexual stage within a freshwater snail host and a sexual stage within the definitive mammalian host; parasite eggs are voided in the urine (eg *Schistosoma haematobium*) or faeces (eg *Schistosoma mansoni*). Despite the availability of adequate tools for diagnosis and treatment, schistosomiasis remains a major public health concern (Savioli et al., 2004). Due to alterations of the environment and increasing migration of man and their livestock, schistosomiasis continues to (re-) emerge. A dramatic example is the outbreak in Northern Senegal in the early nineties. The Diama dam on the Senegal River was constructed in 1985 to produce fresh water for rice and sugar cane agriculture and water supply for municipal use in Dakar. The subsequent ecological changes favored the spread of freshwater snails, followed by a major outbreak of intestinal schistosomiasis (Talla et al., 1990). Soon after, the restricted urinary schistosomiasis foci of the lower delta spread upstream (Verle et al., 1994), and many children can now be found with both urinary and intestinal schistosomiasis.

Praziquantel (PZQ) is the drug of choice to treat schistosomiasis because of the few side effects, the low cost and it is the only drug that is effective against all human schistosome species (Doenhoff et al., 2002). Whereas cure rates for *S. mansoni* usually lie between

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Table 1
Schistosoma mansoni infection intensity (eggs/g) of the children enrolled in the study followed through time. Shaded columns indicate from which time points schistosome populations have been sampled and the darker squares the samples genotyped.

	Timing					
Child ID	**S0**	**S1**	**S2**	**S3**	**S4**	**S5**
1	70	0.0	1200.0	220.0	447.0	1332.0
3	26.7	6.7	600.0	7.0	13.0	84.0
9	146.7	0.0	646.7	0.0	187.0	852.0
11	53.3	0.0	673.3	7.0	193.0	660.0
53	246.7	0.0	320.0	20.0	360.0	132.0
65	366.7	0.0	733.3	13.0	13.0	24.0
49	100	0.0	1126.7	27.0	570.0	2698.0
15	400	33.3	247.0	53.0	107.0	12.0
45	146.7	0.0	944.0	160.0	1053.0	660.0
46	1360	6.7	247.0	93.0	547.0	36.0
73	13.3	0.0	420.0	20.0	600.0	480.0
31	20	0.0	N/A			
85	70	0.0	1200	220	447	1332

S0 = baseline survey (survey and double treatment).
S1 = six weeks post-baseline (survey only).
S2 = six months post-baseline (survey and double treatment).
S3 = six weeks post-S2 (survey only).
S4 = one year post-baseline (survey and single treatment).
S5 = two years post-baseline (survey and single treatment).

70% and 90% (Gryseels et al., 2006), the observed cure rate at the onset of the Senegalese epidemic reached only 18–32% (Stelma et al., 1995). Such a low figure had never been reported elsewhere before and the emergence of resistance was feared. Several alternative explanations have been put forward related to intense transmission and/or the recent nature of the focus, e.g. rapid re-infection, immunological naivety of the human population, and a high number of immature worms (Gryseels et al., 2001, 1994), which are tolerant to PZQ (Sabah et al., 1986). A meta-analysis including PZQ treatment studies from various endemic countries showed that cure rates from Senegal were consistently lower than expected, even when initial infection intensity, follow-up time and sensitivity of diagnosis were accounted for (Danso-Appiah and De Vlas, 2002). Laboratory experiments showed that *S. mansoni* isolated from snails in the epicentre of the *S. mansoni* epidemic were significantly less responsive to PZQ as compared to Kenyan and Puerto Rican strains. They were however fully responsive to the drug oxamniquine (Fallon et al., 1995, 1997), supporting the possibility of PZQ resistance in these Senegalese strains (Fallon et al., 1997). Conclusive evidence for any of the above scenarios has not been obtained so far.

It has been suggested that cure rates may not be a good proxy for drug efficacy against schistosomiasis and soil-transmitted helminths (Gryseels et al., 1994; Montresor, 2011). The standard Kato Katz technique for the diagnosis of *S. mansoni* is not sufficiently sensitive to detect light infections, and cure rates are dependent on baseline/pre-treatment infection intensities. We now have molecular tools to genetically characterize parasite populations. By quantifying neutral genetic variation, we can infer changes in