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Research Note

The wild water-rats and their relevance in the context of schistosomiasis mansoni in Brazil: what we know and recommendations for further research

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Summary

Schistosomiasis is a parasitic and endemic disease in several parts of the world. Its mortality rate reaches alarming proportions, which makes emergency the control of this disease. In Brazil, only the species *Schistosoma mansoni* was adapted to the climatic conditions and to the presence of appropriate hosts. This species shows a life cycle involving mollusks *Biomphalaria* spp. and humans. However, it has been shown that wild rodents with semi-aquatic habits are capable to establish a productive infection of this parasite. In addition, they are likely also to be capable to spread the disease in endemic areas. Due to the selective pressure exerted by the successive infections in these animals, we may be watching the development of a new strain of the parasite, which is not yet fully defined and understood. With the intention of directing new studies to this problem, we tried to establish main lines of research to demonstrate the real importance of these wild rodents in the epidemiology of schistosomiasis mansoni in Brazil.
Keywords: *Schistosoma mansoni*; wild strain; wild rodents

Introduction

Schistosomiasis is a parasitic disease of extreme relevance to public health, caused by trematodes *Schistosoma* sp. (Gryseels *et al*., 2006; Latif *et al*., 2013). Researches show that approximately 240 million people are infected and 700-800 million are at risk of infection (Gryseels *et al*., 2006; WHO, 2015). In Brazil, there are records of transmission of the disease in 18 states of the federation, in addition to the Federal District. The endemic areas are located in the states of Alagoas, Bahia, Espírito Santo, Minas Gerais and Pernambuco, while focal areas are registered in Ceará, Federal District, Maranhão, Pará, Rio Grande do Sul, Rio de Janeiro and São Paulo (Brazilian Ministry of Health, 2014) (Fig. 1). The parasite *S. mansoni* in Brazil has a life cycle that requires the presence of the intermediate host (freshwater mollusks of the genus *Biomphalaria*) and the vertebrate host (i. e. human) (Katz & Almeida, 2003).

The water-rats and *S. mansoni*

Although *S. mansoni* has humans as definitive host, some animals like bovines (Barbosa *et al*., 1962), other primates (Nelson, 1960; Fenwick, 1969), and some species of rodents were found naturally infected (Amorim, 1953; Alarcón de Noya *et al*., 1997). After Cameron (1928) has reported for the first time monkeys parasitized by *S. mansoni*, a long time passed until the wild rodents were also detected with natural infection, both in Africa and Brazil (Amorim, 1953; Kuntz, 1962). Some of these rodents in Brazil are shown in Table 1.

Among these rodents, the genera *Nectomys* and *Holochilus* stand

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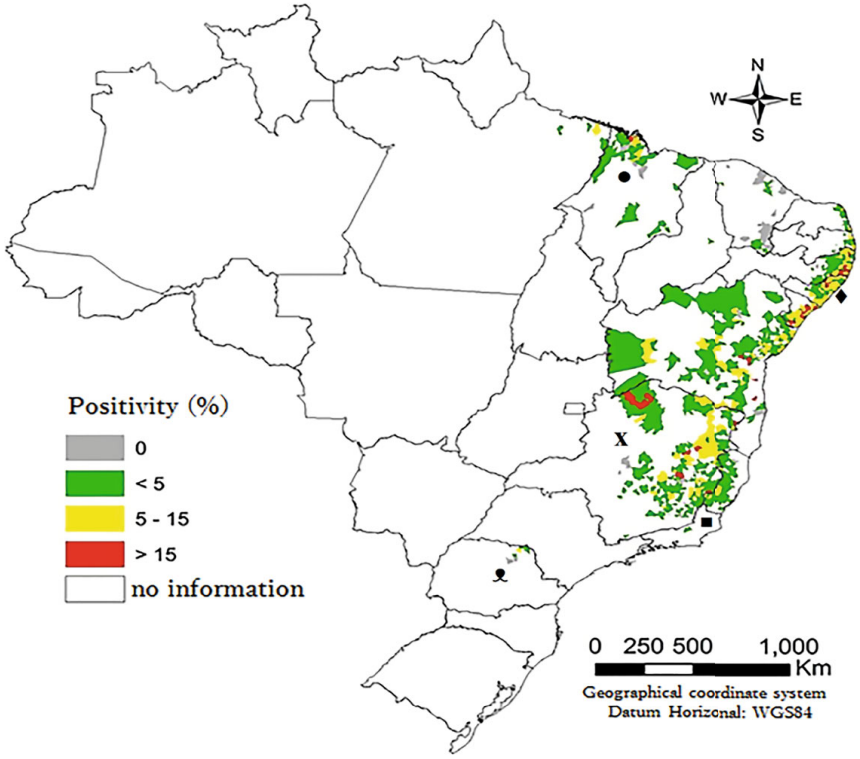

Fig. 1. Prevalence for *S. mansoni* in Brazil (2010 – 2015). (Brazilian Ministry of Health, 2014)
Some states where naturally infected wild rodents have been found are marked by symbols (● Maranhão; ♦ Alagoas; **x** Minas Gerais; ■ Rio de Janeiro; Paraná)

out, due to some factors such as: tolerance to human presence, occurring in the peridomicile and their semiaquatic habits, a preponderant factor for the infection by the cercariae of *S. mansoni* (Ernest & Mares, 1986; Mello, 1986). The infection in these animals shows that they were not strongly affected by parasitism and elimination of viable eggs was constant during the whole infection period (Machado-Silva *et al*., 1994). Highly susceptible to various strains also was demonstraded (Rodrigues-Silva *et al*., 1992; Martinez *et al*. 2008).

According to Martins (1958), in order to have a real parameter of the importance of these wild reservoirs in the epidemiology of schistosomiasis, it is necessary that studies are based on the following objectives: a) To determine the relative susceptibility of rodents that are frequently found with natural infection in different endemic areas, performing serial euthanasias to establish the number of infected and uninfected animals; the number, sex, stage of maturation of worms; size and location in the host body; presence of viability and non-viability eggs in different organs, feces and urine; and duration of infection; b) To infect mollusks with miracidia from eggs obtained from naturally infected rodents and to perform infection on laboratory and wild animals with cercariae of these mollusks; c) Determine whether these rodents are capable of maintaining the infection in the absence of infected humans. d) Determine if the man is susceptible to strains of the parasite from wild animals using human volunteers. However, there could be ethical problems in this type of research.

Following this suggestive list of requirements for a possible framing of these wild rodents as true wild reservoirs of *S. mansoni* in Brazil, several studies were conducted in order to elucidate some of these points suggested by Martins (1958). As a consequence of these facts, some authors like Piva *et al*. (1966) and Souza *et al*. (1992), carried out experimental infections in rodents *Holochilus* sp. and *Nectomys* sp., which observed that, during eight months of infection, there was an average elimination of 1,000 eggs/day by these animals. According to several protocols, have demonstrated that during four months of experimental infection, the mollusks *B. glabrata* could be effectively infected through miracidia that came from the feces of these rodents (Picot, 1992). Gentile *et al*. (2010), in parasitological researches with *N. squamipes*, proved that under natural conditions, *S. mansoni* infection does not affect the survival, reproductive capacity and mobility of the animal, allowing continuity of the helminth cycle. In experiments performed in seminatural conditions, Kawazoe & Pinto (1983) demonstrated that *Holochilus* sp. was capable to maintain the cycle of the parasite in the absence of man when the intermediate host was *B. glabrata.*

Table 1. Some species of wild rodents that were found naturally infected with *S. mansoni* in Brazil

Region	State	Wild rodents	Infected (%)	Authors
Southeastern	Minas Gerais (Belo Horizonte)	*Orthoptera mattogrossae*	100	Martins *et al*. (1955)
		Nectomys squamipes aquaticus	57.5	
		Rattus norvegicus norvegicus	46.8	
		Cavia aperea aperea	33.3	
		Oryzomys subflavus	12.0	
		Zygodontomys lasiurus	2.7	
	Rio de Janeiro (municipality of Sumidouro)	*N. squamipes*	34.5	Maldonado-Júnior *et al.* (2006)
South	Paraná	*N. squamipes*	18.18	Luz *et al*. (1966)
Northeast	Alagoas	*N. squamipes*	45.31	Amorim (1953)
		Holochilus sciureus	25.0	
		Oxymycterus angularis	11.11	Amorim *et al*. (1954)
		Zigodontomys pixuna	1.78	
		Or. subflavus	1.03	
	Baixada Maranhense (municipality of São Bento)	*Holochilus* sp. (probably *H. sciureus*)	29.6	Veiga-Borgeaud *et al*. (1986)
			28.7	Miranda *et al*. (2015)
			23.8	Lira *et al*. (2016)

The wild and human strain

Since the discovery by Amorim (1953) that these wild rodents could maintain a productive infection by *S. mansoni*, Kloetzel (1959) began the suspicions of the existence of two distinct strain, which were called years later by Bastos *et al*. (1978) as human (H) and wild (S) strain. The first studies were started with the finality to explore specific characteristics of each isolate to verify possible phenotypic plasticity induced by the selective pressure of these rodents as new potential reservoirs of the parasite, because according to Cioli *et al*. (1977), the different vertebrate hosts strongly determine differentiated morphological characteristics in *S. mansoni* adult worms.

From this, different studies were carried out to determine if these changes could be useful to distinguish effectively the S and H strain, because these differentiated taxonomic characteristics could be used as a marker in epidemiological surveys of *S. mansoni* infection in areas with both human and wild rodents naturally infected, which could provide information about the actual contribution of these animals to infection rates in the human population (Rey, 1993).

Despite the controversies, some studies have shown that male adult worms from natural infections in *N. squamipes* were larger than those from H strain infections (Machado-Silva *et al*., 1994). However, the findings of Neves *et al*. (1998) described different morphometric conditions, since male adult worms (isolated from *N. squamipes*) showed smaller measures than H strain, whereas adult female worms showed longer lengths. The number of testis in adult male worms also showed some alterations when originating from S strain, being reported differences in number and location (Machado-Silva *et al*., 1995). In addition, significant differences were also observed in adult male parasite in relation to the total length and the distance between the oral and ventral suckers, when compared to several Brazilian strains from humans (Machado-Silva *et al*., 1995). In natural infections in *H. b. leucogaster* (Brandt, 1827) captured in the São Paulo state, Dias & Piedrabuena (1980) observed that adult worms and *S. mansoni* eggs analyzed did not present differences when compared to classic human isolates of the parasite.

In the Maranhão state, more precisely in the Baixada Ocidental Maranhense, some rare and old studies also proposed to establish possible differences between these strains. According to Bastos *et al*. (1982), when they verified the virulence pattern of S and H strains (from Maranhão) in *B. glabrata* collected in the same area of occurrence of naturally infected rodents, it was observed that S strain was three times more virulent than H strain. For the authors, these data strongly suggest that there are sufficient reasons to demonstrate that the two strains have some level of isolation in the nature, due to the existence of differences to the parasitological behavior in mollusks. In addition to this research, Carneiro *et al*.

(1991a) and Carneiro *et al*. (1991b) also observed differences between the S and H strains through antigenic fractions obtained by Western blot methodology. Among the most recent studies, only Ferreira (2012) followed this same proposal, by analyzing the mitochondrial genes of the parasite, cytochrome c oxidase subunit 1 (cox1) and cytochrome b (cob), which after sequencing, alignment and editing, observed that the cob gene, the most variable, it was possible to verify differences between S and H strain.

Although the evidence is beginning to be elucidated in the last century, there was a great scientific gap without studies that continued the proposal of differentiation the two strains. With the advent of modern methodological tools, the question of their existence or not would be easily solved. Currently, Brazil is experiencing a reduction in transmission rates of schistosomiasis, with an increase areas of low endemicity, in this sense, several studies are directed to establish new diagnostic methods that are more sensitive and specific to detect these areas. However, who knows the presence of the wild strain in some regions of Brazil are not providing a difficulty in a more accurate diagnosis? From that Brazil's situation, we elaborate a bulleted summary of the main lines of research that should be addressed by the researchers:

- Isolation of antigens from the adult worm (SWAP) or eggs (SEA) of wild strain for differential diagnosis in humans (more refined genetic studies would also be important in this case);
- Analyze the type of immune response (innate and acquired) that is developed against the wild strain of *S. mansoni*;
- Despite low infections in humans these rodents (mainly *Holochilus* sp. and *Nectomys* sp.) remain highly parasitized. The position of these rodents in schistosomiasis transmission needs to be elucidated in further epidemiological studies.

In conclusion, we believe that these are the most urgent questions to be addressed in further research in order to have the real importance these wild water-rats in the epidemiology of schistosomiasis in Brazil.

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