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Efficacy of Mass Drug Distribution (MDD) in National Schistosomiasis Control Programme Sentinel Sites in Mali

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Abstract: Background – Mali was one of the first countries in sub-Saharan Africa to initiate a national schistosomiasis control programme (NSCP) in 1982. The WHO's 2021-30 roadmap sets out criteria for eliminating and controlling schistosomiasis as a public health problem. Our study aimed to assess the impact of annual Mass Drug Distribution (MDD) with praziquantel (PZQ) among school-age children in the sentinel sites (SS) of the NSCP. **Methods** –The study took place at twelve SS in Kayes and Koulikoro regions. Two-round observational cross-sectional studies were carried out in December 2014-2015 and in April 2018 after four to five years of annually MDD. Overall, 2442 schoolchildren aged 7 to 14 were successfully examined. The urine filtration and Kato-Katz method were used for determining *Schistosoma haematobium* and *S. mansoni* eggs, respectively. **Results** –Of the twelve SS treated from 2014-2015, one has achieved the criterion of elimination of *S. haematobium* as a public health problem (prevalence of heavy intensity infection PHI < 1%) (ie, ≥50 *S. haematobium* eggs per 10 mL of urine or ≥400 *S. mansoni* eggs per g of stool), four met the morbidity control criterion (PHI< 5%) while two sites remained confined below the morbidity control criterion (PHI>5%). Five SS had no heavy intensity infection. The prevalence of S. mansoni was less than 1%. **Conclusion** –The impact evaluation of MDD with praziquantel in the SS of NSCP highlights that MDD has significantly reduced the PHI of schistosomiasis. However, the high prevalence of schistosomiasis or its increase in some sites requires in-depth studies.

Keywords: Schistosomiasis; Mass Drug Distribution; Sentinel sites; Mali

1. Introduction

Schistosomiasis is one of the most important human helminthiasis in terms of morbidity and mortality (McManus & Loukas, 2008). The disease is endemic in many developing countries mainly affects children, farmers, and women who are frequently in contact with water inhabited by snail intermediate hosts. According to the WHO, in 2019, 236.6 million people will need preventive treatment in 78 countries (Ossai et *al.*, 2014; WHO 2022), with the heaviest burden in sub-Saharan Africa (90%) (4).

According to the results of the national surveys carried out by the Schistosomiasis National Schistosomiasis Control Programme (SNCP) in 1984-1989, then in 2004-2006, schistosomiasis due to *Schistosoma mansoni* and *S. haematobium* and Soil-transmitted helminths (STH) are still endemic throughout the country (5). For instance, in 2004, the prevalence of *S. haematobium* and those of *S. mansoni* were 61.7% and 12.7% respectively in the Office du Niger irrigated area (6). Along the Senegal river, the prevalence were higher than 70% in some villages (7)

Recommended by the WHO from 1970 to 1980 (8,9), large-scale chemotherapy to control morbidity with coverage rate of 75% in school-age children have been formally considered as an essential public health strategy to combat schistosomiasis by the fifty Fourth World Health Assembly (WHA 54.19) in 2001. As indicated in the WHO guidelines, a new initiative to resume the national

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control activities has been in place in Mali since 2004, targeting school-aged children (SAC) and adults at risk in order to achieve the WHA54.19 recommendation with technical and financial support from the Schistosomiasis control Initiative (SCI), USAID/RTI/HKI, The organization for the development of the Senegal River (OMVS) and Sight savers in all endemic regions (10,11). Following this initiative, MDA with PZQ, four regions first benefited from the strategy in 2005, targeting only school-age children (7–14 years old) attending schools. By 2006, the strategy was expanding to other regions, targeting all school-age children (5–15 years old) (11). In 2007, the Schistosomiasis and Soil-transmitted National Control Programme (SNCP) devoted to combat schistosomiasis were integrated into the National NTDs Control Programme. Since that date, an annual or bi-annual treatment campaign carried out in all endemic areas (Ségou, Mopti, Koulikoro and Kayes regions) based on the current prevalence threshold as recommended by the WHO. However, since the NSCP has adopted the community directed intervention (CDI) approach in 2005, the programme has faced some difficulties which led to very low coverage, particularly in some endemic areas such as the Diéma district in Kayes region. In addition to these difficulties, its impact needs to be assessed regularly, particularly in sentinel sites. The current study was carried out with a view to a global fight against schistosomiasis in line of the WHO's 2021-2030 road map to achieve the target for eliminating schistosomiasis as a public health problem and the interruption of transmission in humans in selected countries adopted in 2022. It aimed to assess the impact of MDA with PZQ on the prevalence and intensity of schistosomiasis and STH in sentinel sites identified by Schistosomiasis National Control Programme (SNCP).

2. Materials and Method

2.1. Study Site

The study was carried out in twelve villages spread over six districts: Bafoulabé, Diéma and Kayes (in Kayes region); Kalabancoro, Koulikoro and Nara (in Koulikoro region) (Figure 1). The Hydrographically network in the study is made up of Senegal River and its tributaries in Kayes region, and Niger River and its tributaries in Koulikoro region. It also composed by the lake system (Lac Magui) and pools (Doro and Goumbaye) in the Kayes region. The economic life in the study area is dominated by agro-pastoral activities which occupy more than 80% of the population. The health system is precarious, with high infant and maternal mortality, low life expectancy, chronic malnutrition among children and inadequate infrastructure and equipment (12). The study site is recognized as a highly endemic area for schistosomiasis (8,13,14). The Kayes region, particularly the Diéma district, is characterized by a low treatment coverage rate of less than 60% ((oral communication from the PNLSH's coordinator).

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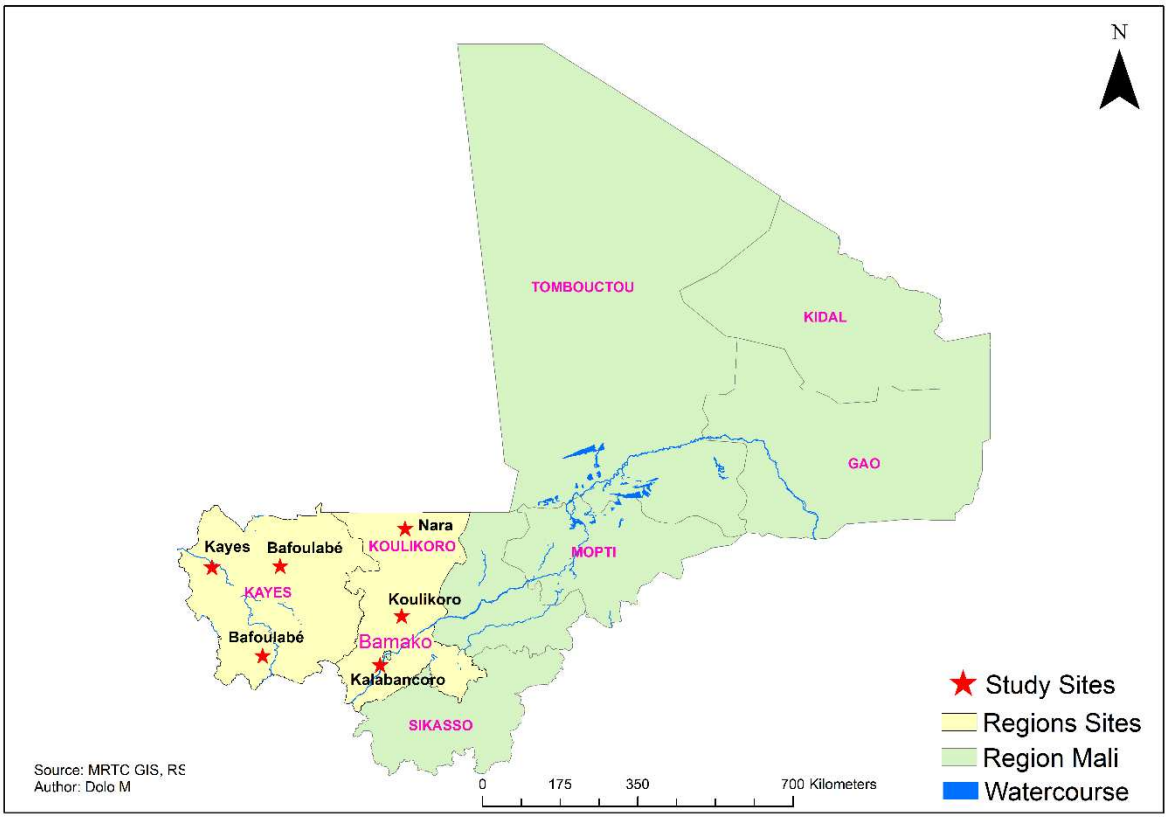

Figure 1. The map of Mali showing the localization of study sites (*).

2.2. Population and Study

School-aged children 6- to 14 years old were primarily identified as study population. We carried out a two-round observational cross sectional study: the first baseline round was conducted in December 2014-2015 and the second in April 2018. According to SNCP officials, from December 2014-2015 to April 2018, children were regularly submitted to MDA with PZQ. During each pass, stool and urine samples were examined. The time lag between the different treatment rounds is due to the treatment agenda of the SNCP in relation to each district planned treatment frequency.

2.3. Sampling Design and Sample Size Calculation

For the 2018 study students were randomly selected from schools from the list of students present in each class on the day of the survey. A random draw without discount was adopted for the selection of participants. The sample size was calculated on the basis of the prevalence of *S. haematobium* (the most frequent schistosome species) described in 2009. The assumed precision around the prevalence rates to be measured was 6% with an alpha risk of 5%. We added 10% to this sample size to compensate for the loss of sight. The Schwartz formula was used to calculate the minimum sample size. The results of this study were compared to those of 2014-2015 carried out by the NSCP. According to the officials of the programme, the sample size examined in 2014-2015 (n=720) was calculated according to WHO sample size estimation (15).

2.4. Data Collection Techniques and Procedures

All urine samples were collected between 10.00 am and 2.00 pm in the field, by trained laboratory technicians to determine prevalence and intensity of *S. haematobium* infection. Urine was collected from each subject in a properly labeled specimen container. Filtration technique was used to analyse the samples. A total of 10 ml of urine was taken from each specimen bottle after mixing it. The mixed sample was filtered through a Whatman filter (CAT N° 1001-025, 25 mm) which was

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stained with 3% ninhydrin solution, before being sent to Bamako to be examined under a microscope using ×10 magnifications for *S. haematobium* egg characteristics. One single stool sample from each child was collected and examined immediately on fields with the standard Kato-Katz method for *S. mansoni* and STH eggs. The intensity of *S haematobium* infection was expressed as the number of eggs per 10 ml of urine and was classified into three categories: i) no egg; ii) slight (1–49 eggs per 10 ml of urine); and iii) heavy (≥50 eggs per 10 ml of urine). The intensity of *S. mansoni* intensity was expressed as eggs per gram of stool (pg) and classified into four classes: *i*) no egg; *ii*) 1–99 EPG (eggs per gram of stool); *iii*) 100–399 EPG; and *iv*) ≥ 400 EPG (11). To ensure quality control, 10% of the filters and slides were randomly selected and recounted by another senior biologist. At the end of the study, all the positive children were treated with PZQ (40 mg/kg body eight) according to the Schistosomiasis and STH National Control Programme in Mali (PNLSH).

2.5. Mass Drug Administration

The preventive chemotherapy strategies recommended by the WHO has been adopted by the Mali's schistosomiasis control programme since 2005 in four endemic areas (8,12) . To perform this strategy, a MDA campaign is designed each year in schools and health authorities at regional, district and community school personal are mobilized. Drugs are distributed through the school-based delivery in schools targeting school-going children. This drug delivery strategy is carried out by trained school teachers. PZQ tablets (600 mg) were delivered using the WHO dose pole method to determine the dosage for each child (16). Current WHO guidelines (17) use heavy-intensity infections (≥50 *S. haematobium* eggs per 10 mL of urine or ≥400 *S. mansoni* eggs per gram of stool (12) to categorize a target population's status. Target populations with a prevalence of heavy-intensity infections (PHI) <5% are classified as having controlled schistosomiasis morbidity, and when a target population has <1% PHI, that population has eliminated schistosomiasis as a public health problem.

2.6. Ethics

Before currying out the survey in each sentinel school, informed verbal consent was first obtained from the schoolteachers before the children were recruited. These were recorded by the survey team leader. During recruiting, informed verbal consent was obtained from each child with the presence of the school teachers. Any children who did not wish to participate were free to leave without prejudice to their support for the treatment. Study participants who tested positive for *S. haematobium* or *S. mansoni* were treated with praziquantel at the standard dose of 40 mg/kg body weight as recommended by the SNCP. The drug was administered orally after the child had eaten. The proposal was reviewed and approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Pharmacy and Dentistry of the University of Bamako (N°2017/135/CE/FMPOS).

2.7. Statistical Analysis

Data were entered in duplicate using Access and Prevalence, and intensity of infection with 95% confidence intervals was calculated using SPSS (IBM, version 19). Differences in proportions were tested using the chi-square test or Fisher's exact test depending on the data. P values less than 0.05 were considered to be significant.

3. Results

In December, 734 schoolchildren were examined with320 females and 414 males. In April 2018, 1836 schoolchildren have been screened from which 1708 were successfully examined including 733 females and 975 males. They were aged between 7 to 14 years with an average age of 9 ± 1.970 years. As shown in the Table 1, *S. haematobium* prevalence in 2014 varied from zero in Boudjiguiré to 96.8% in Babaroto. In 2018, the prevalence increased to 11% in Boudjiguiré while it decreased significantly to 33.95% in Babaroto (*p<0.001*). Overall, from 2014 to 2018, the prevalence decreased significantly in Babaroto, Saorane, Torodo and Koussané (p< 0.001) and Dianguirdé (p=0.004), increased

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significantly in Diakalel (p<0.001), but not significantly in Kolly and Boudjiguiré (*p>0.05*). From 2015 to 2018, the prevalence increased significantly in Samaya (*p=0.006*) and Kokoun (*p=0.02*) (Table 1).

Table 1. Variation in the prevalence of *S. haematobium* (in % in parenthesis) in the sentinel schools/Villages in the Kayes and Koulikoro regions from 2014- 2015 to 2018.

		Periods				
District	**Sentinel sites**	**2014**	**2015**	**2018**	**Diff. (%)**	***p***
Bafoulabé	Babaroto	62 (96.8)		78 (62.8)	33.95	*<0.001***
	Saorané	60 (70.0)		108 (31.5)	38.51	*<0.001***
Diéma	Dianguirdé	60 (76.7)		184 (54.3)	22.32	0.004**
	Torodo	60 (80,0)		169 (39.6)	40.36	*<0.001***
Kayes	Diakalel	63 (31.7)		226 (84.1)	- 50.55	*<0.001***
	Koussané	60 (65.0)		109 (32.1)	32.89	*<0.001***
Koulikoro	Dougourakoro		60 (5.0)	65 (7.7)	- 0.03	*0 .8036**
	Kokoun		60 (16.7)	160 (34.4)	- 17.71	*0.02***
	Kéniégoué		63 (1.6)	214 (7.4)	- 5.89	*0.16**
	Samaya		63 (1.6)	183 (15.9)	- 14.26	*0.006***
	Kolly	60 (8.3)		103 (15.5)	- 7.2	*0.28**
	Boudjiguiré	63 (0)		109 (11.9)	- 11.9	*0.011***

** Statistically significant p-value (p<0.05); * Statistically non-significant p-value (p>0.05).

Between 2014 to 2018, there was a significant reduction in the prevalence of heavy intensity infection with *S. haematobium* in the districts of Bafoulabé (Babaroto and Saorané) and Diéma (Dianguirdé et Torodo) (*p<=0.001*) (Table 2). In Diakalel, the prevalence of heavy infections rose to 19.21% from 2014 to 2018 (*p<0.001*). In Kolly and Bougoudjiré, the prevalence remained zero. From 2015 to 2018, the prevalence of heavy infections increased slightly in Dougourakoro and Samaya, decreased slightly in Kokoun.

In terms of results obtained after treatment campaigns on the intensity of the disease, one SS (Saorané) have achieved the criterion of eliminating schistosomiasis as a major public health problem (prevalence of heavy intensity infection - PHI< 1%); four sites (Dianguirdé, Torodo, Koussané and Kokoun) have reached the criterion for controlling morbidity (prevalence of high excretors - PHI< 5%) and two sites (Babaroto and Diakalel) remain confined below the control criterion

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(PHI>5%). The status of five SS (Dougourakoro, Keniegue, Samaya, Kolly and Bougoudjire) without any havy intensity infection in 2004 did not change in 2018.

Table 2. Variation in the prevalence of high intensity *S. haematobium* infections (% in parenthesis) in sentinel sites of Kayes and Koulikoro between 2014- 2015 and 2018.

		Periods				
District	**Sentinel sites**	**2014**	**2015**	**2018**	**Diff. (%)***	**p**
Bafoulabé	Babaroto	62 (29.0)		78 (9.0)	20.06	*0.004***
	Saorane	60 (13.3)		108 (0)	13.0	*0.0004***
Diéma	Dianguirdé	60 (26.7)		184 (3.3)	23.41	*<0.001***
	Torodo	60 (25.0)		169 (4.7)	20.27	*<0.001***
Kayes	Diakalel	63 (1.6)		226 (20.8)	-19.21	*0.0007***
	Koussane	60 (8.3)		109 (1.8)	6.5	*0.10**
Koulikoro	Dougourakoro		60 (0)	65 (1.1)	- 1.5	*1*
	Kokoun		60 (3.3)	160 (1.9)	1.46	*0.89**
	Keniegue		63 (0)	214 (0)	0	--
	Samaya		63 (0)	183 (0.5)	0	*1*
	Kolly	60 (0)		103 (0)	0	--
	Boudjiguiré	60 (0)		109 (0)	0	--

** Statistically significant p-value (p<0.05); * Statistically non-significant p-value (p>0.05).

4. Discussion

This study aimed to assess the impact of the repeated MDA with Praziquantel in twelve sentinel sites among two *S. haematobium* endemic areas (Kayes and Koulikoro) covered by the National Schistosomiasis Control Programme (NSCP). Children aged between 6 and -14 were identified as targeted population in regard to the peak prevalence and intensity of schistosomiasis and STH observed in this age group (12). The priority given to this age group is based on the fact that the level of infection observed in this population reflects the impact of several round of MDD with PZQ after the implementation of a control programme. In line of WHO current road map guidelines (2021-2020), only one and four out of the twelve SS reached the elimination and morbidity control of schistosomiasis criterion as public health problem (PHI<1% and PHI<5%, respectively) in 2018 after four to five MDD rounds. Reducing the prevalence of heavy infection is important as it is well known that the severity of morbidity caused by schistosomiasis is closely related to the intensity of infection. In many national control programme, cases of severe morbidity were avoided or reversed with MDA. This is in line with what was achieved in other national MDA programme particularly in East and West Africa through preventive chemotherapy (18–22). However, beside the heavier infections, there still exist a significant proportion of children with infections of relatively low intensity (1-49 eggs per 10 ml of urine), not counting those who were not detected due to the low sensitivity of the urine

filtration technique. This is the case of the five sites (Dougourakoro, Keniegue, Samaya, Kolly and Boudjiguiré) where no heavy-intensity infection were observed in 2014-2015. Such low intensities of infection have long been overlooked in terms of the morbidity consequences, while recent findings suggest that light infections can cause considerable morbidity due to anaemia, chronic pain, diarrhoea, exercise intolerance and undernutrition (23). Anyway, the objective of MDD was to prevent morbidity due to schistosomiasis by regular treatment in line with WHO recommendations (12,24) as it was conducted in the sentinel sites. In other hand, in contrast to the low success rate in eliminating as a public health issue (one and four SS with PHI<1% and 5% for schistosomiasis elimination and control, respectively), the prevalence of infection was significantly reduced at 66.7% (8/12) sites. In view of the performance of such results, some authors suggested a reevaluation of the criteria for schistosomiasis control because of the inability of current PHI categorizations to differentiate the prevalence of standard morbidity markers. To this end, they propose to shift the definition of the schistosomiasis elimination as public health (EPHP) targets to a function of the prevalence of any *Schistosoma* infection rather than its intensity (25). Persistence or increase of infection in some SS (Table 1) emphasizes in line with World Health Organization (WHO) guidelines the need for a more effort associating with comprehensive control measures including reinforcement of preventive chemotherapy, intensified case management, snail's intermediate hosts control, health education and improvement of sanitation and access to improved water sources, sanitation and hygiene (26,27). Another hypothesis in addition to the low impact of treatment would be the hybrid strains of *S. haematobium* /*S. bovis* or *S. haematobium*/*S. curassoni* identified in the study site (28) and which have been found to influence parasite establishment, growth, maturation, reproductive success, and/or drug efficacy (29,30). Our study is limited by the amount of urine (10ml) or feces (25mg) examined from the filtration of a single urine sample (10 mL) or the examination of a single feces sample (25 mg of feces) with Kato-Katz technique. The two surveys (2014-2015 and 2018) although conducted by two different teams do not call into question the validity of the results obtained. The impact of MDD with PZQ resulted to a significant reduction of prevalence and intensity of infection in the NSCP SS after four to five treatment rounds. The persistence of the disease or its increase some other sites call for further investigations, including the existence of hybrid strains and their role in public health.

5. Conclusions

The study assessed the impact of MDD with PZQ over a period of four to five years in twelve sites sentinel of the NSCP. Despite repeated treatment campaigns, schistosomiasis remains hyperendemic (P>50%) in some sentinel sites such as Diakalel and Babaroto and hypoendemic (P<10%) in others such as Keniegue and Dougourakoro. One SS reached the criterion for schistosomiasis elimination as public health problem (PHI<1%) while four achieved the criterion of morbidity control (PHI<5%) in line of WHO's 2021-2030 road map. However, two sites remain confined below the control criterion (PHI>5%). These results call for a major improvement in therapeutic coverage in addition to intensified case management, sanitation and hygiene to interrupt the schistosome transmission cycle.

Author's contributions: A.D. has updated the research methodology. A. D., A.P., D. M., D. S., D. S., coordinated the fieldwork. A. P., D. M. and A. D. read the filters and slides. A. P. and A. D. carried out the statistical analysis. A. P., D. M., A. D. and I. M., reviewed the manuscript prior to submission.

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Conflicts of interest: No conflicts of interest.

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