PLOS ONE

RESEARCH ARTICLE

Schistosomiasis and soil-transmitted helminthiasis preventive chemotherapy: Adverse events in children from 2 to 15 years in Bengo province, Angola

Manuel Lemos[1,2,3], Joao M. Pedro[1,2]*, Cláudia Fançony[1,2], Sofia Moura[1], Miguel Brito[1,4], Susana Vaz Nery[5], Carlos Pinto Sousa[3], Henrique Barros[2,6]

1 CISA—Centro de Investigação em Saúde de Angola, Caxito, Angola, **2** EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal, **3** Departamento de Saúde Pública, Faculdade de Medicina, Universidade Agostinho Neto, Luanda, Angola, **4** H&TRC—Health and Technology Research Center, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal, **5** Kirby Institute, University of New South Wales, Sydney, Australia, **6** Faculdade de Medicina, Universidade do Porto, Porto, Portugal

* joao.almeidapedro@cisacaxito.org

Citation: Lemos M, Pedro JM, Fançony C, Moura S, Brito M, Nery SV, et al. (2020) Schistosomiasis and soil-transmitted helminthiasis preventive chemotherapy: Adverse events in children from 2 to 15 years in Bengo province, Angola. PLoS ONE 15(3): e0229247. https://doi.org/10.1371/journal.pone.0229247

Editor: Mary Hamer Hodges, Helen Keller International, SIERRA LEONE

Received: October 29, 2019

Accepted: January 29, 2020

Published: March 11, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0229247

Data Availability Statement: The anonymised data set is freely available in Zenodo database (DOI: 10.5281/zenodo.3660023).

Abstract

Preventive chemotherapy campaigns with praziquantel and albendazole are being implemented in Angola, as a high priority public health intervention. However, there are no published data regarding adverse events associated with these medications. In this context, we analysed adverse events due to co-administration of praziquantel and albendazole in endemic areas of schistosomiasis and soil-transmitted helminths in Bengo, Angola. In the context of a targeted drug administration, between December 2012 and September 2013, we conducted two surveys after co-administrating single oral doses of praziquantel and albendazole tablets to children 2 to 15 years of age. About 24 hours after each treatment, participants answered a questionnaire about adverse events. At baseline, 605 children (55.0% male; mean age: 9.7 years) were treated; 460 were interviewed and 257 (55.9%) reported at least one adverse event, 62.3% (160/257) of children being infected with *schistosoma haematobium*. After six months of treatment, among 339 children surveyed, 184 (54.3%) reported adverse events, with 49.5% (91/184) of infected children. Adverse events were most common in preschool-aged children, with no significant difference between genders. The most frequent adverse events in the two surveys were abdominal pain (18.5%, 25.7%), headache (20.9%, 23.0%) and dizziness (15.7%, 19.8%). Children aged 12 to 15 years (adjusted OR = 0.40, $p = 0.040$) and those with mixed infection (adjusted OR = 0.04, $p = 0.011$) had lower odds of adverse events. After the second treatment, those with heavy infection (adjusted OR = 2.72, $p = 0.018$) and aged 9–11 years (adjusted OR = 2.01, $p = 0.049$) had significantly fewer adverse events. About 2.0% of children experienced severe adverse events. This study adds evidence that preventive chemotherapy for schistosomiasis and soil-transmitted helminths control is safe, but cases of adverse events are expected. Standardized methodologies to discriminate drug-related adverse events from the clinical manifestations of the infections are needed.

Funding: This work was supported by the promoters of the CISA as follows: Camões, Institute of Cooperation and Language, Portugal (www.instituto-camoes.pt/en/); Calouste Gulbenkian Foundation, Portugal (https://gulbenkian.pt/en/); Government of Bengo Province; Angolan Ministry of Health (www.minsa.gov.ao). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors declare no competing interests financial or nonfinancial with regards to this study. The interpretation of data and presentation of information is not influenced by any personal or financial relationship with any individual or organization.

Introduction

Neglected tropical diseases (NTD), including schistosomiasis and soil-transmitted helminths (STHs), remain important public health issues in developing countries, where lack of adequate clean water and poor sanitation are common [1–3]. Schistosomiasis is one of the most socio-economically devastating parasitic disease in the world, causing estimated 280 thousand deaths and 4.5 million Disability Adjusted Life Years (DALYs) [4]. On the other hand, STHs, namely infections by *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms, affect more than one billion individuals worldwide, causing respectively, 60, 10 and 65 thousand deaths, respectively [5,6]. In Angola, the prevalence of those diseases are high and variable within the country [7]. Recently, in a community based survey conducted by Figueiredo *et al* [8] in the Dande municipality (northern Angola), prevalence of urogenital schistosomiasis in preschool-aged children (PSAC) and school-aged children (SAC) were reported to be 10% and 17%, respectively, with 10% of anaemia cases in the studied population. The same study determined the prevalence of infection by at least one STH of 22.6% in preschool-aged children and 31.6% in school-aged children in the Dande municipality [8]. Another study conducted in the same region found an association between *A*. *lumbricoides* infection and malnutrition in children [9].

Preventive chemotherapy (PC) refers to the periodic administration of anthelminthic drugs to populations at risk of morbidity, with the aim to reduce infection intensity and eliminate moderate and heavy infections [10]. Thus, mass drug administration (MDA) is the cornerstone of the current global strategy to control helminthiasis. In children aged 2 to 15 years, Schistosomiasis is recommended to be controlled by taking a single dose (40mg/Kg child weight) of praziquantel (PZQ) and STHs with a single dose (400mg) of albendazole (ALB) [11]. ALB has a remarkable safety record, considering that a very low frequency and incidence of adverse events (AEs), mainly gastrointestinal, are described in the literature [12,13]. On the other side, despite that minimal and transient adverse events are described to occur with PZQ (reported mainly in heavily infected people and normally associated to the response of the host immune system to the dying worms), serious adverse reactions can also take place and may reduce drug compliance [13–21]. In fact, AEs resulting from co-administrating both drugs are described to be similar in severity to those experienced with monotherapy, however, information regarding the safety of this combination in children under 4 years of age (or under 94 cm in height) is scarce, especially in Angola [22]. As a consequence, preschool-aged children (PSAC) were considered ineligible for MDA with PZQ and the control approach were the referral to health facilities for individual case management [11].

According to WHO guidelines [10,11], AEs occur 24–48 hours after drug administration but do not necessarily have a causal relationship with treatment. They may be mild when not affecting daily activities (e.g. playing) or moderate when affecting the performance of daily activities. However, severe AEs require complete rest and / or medication, while serious AEs are life-threatening and require admission to the hospital.

In 2010 WHO recognized that preschool-aged children were a high-risk group for schistosomiasis (when living in highly endemic settings), that should also be included in public health interventions, along with school-aged children and woman in childbearing age [15,23]. This was followed by several reports on the safety of PZQ in preschool-aged children (between 1 month and 7 years) and the recognition that administrating PZQ to those children was safe and efficacious [11,18,23–25]. Nevertheless, Angola is an endemic country for schistosomiasis and STHs and the therapeutic policy for those diseases is presently aligned with the 2006 WHO guidelines [11]. Currently, and at a national level, diagnosed cases of schistosomiasis in school-aged children are recommended to be medically treated at health care units and control activities for STHs are based in deworming campaigns [7,11].

Therefore, further evidence on adverse events (AEs) to the co-administration of PZQ and ALB, experienced in the context of TDA campaigns, are needed. Additionally, there is no published data in Angola regarding adverse events associated to the co-administration of PZQ and ALB, either in preschool-aged (particularly in under 4) or school-aged children. Thus, considering that the local health authorities of the NTD control program are implementing regular helminth control campaigns, these data are essential to inform these programs and to fill the treatment gap for children under 4 (currently excluded from TDA and often neglected).

Consequently, this pioneering study was carried out in the community of Cabungo and the Porto Quipiri School, located in the study area of the CISA project (Angola Health Research Centre, translated). We aimed to analyse the adverse events experienced following co-administration of PZQ and ALB for preventive chemotherapy against schistosomiasis and STHs.

Methods

Study site

We conducted this study between December 2012 and September 2013, in Cabungo community and Porto Quipiri School, located in the study area of CISA, in the Dande Municipality, Bengo Province—northern Angola. These hamlets were selected due to high prevalence of SCH, STHs and malaria observed in the area, whose structure, dynamics and geographical distribution of the population was previously described by Costa *et al* (2012) [26] and the epidemiology of schistosomiasis and STHs was detailed recently by Sousa-Figueiredo *et al* (2012) [8].

Study design and aim

This is a longitudinal study, conducted in the context of a plan intervention by local health authorities, aiming to investigate the adverse events experienced by PSAC and SAC following the mass drug co-administration of PZQ and ALB, for the control of schistosomiasis and STHs at baseline and 6 months after the first treatment.

Participants and therapeutic intervention

For this study, we enrolled 605 children, of whom 460 (76.0%) and 339 (56.0%) successfully participated in the first and second survey for AEs, respectively. All children, aged between 2 to 15 years old and living in those areas, were invited to participate and received a kit containing single doses of PZQ (40mg/kg), using the dose pole method to determinate the number of PZQ tablets to be administered to each child, and single doses of ALB (400mg) tablets. The tablets were crushed or broken when necessary and given with water or juice, as recommended by others [26], taken under direct observation of a health professional onsite. We also timely treated, with artemeter-lumefantrine (AL-20/120mg), children tested positive for malaria as recommended by the National Malaria Control Program [27]. In addition, refusals or failure in successful administration was documented. We excluded children if any severe adverse events were reported to be experienced in previous administration of PZQ and ALB.

Laboratory analysis

Pre-treatment stool samples were collected for the diagnosis of intestinal parasites (*Schistosoma mansoni*, hookworms, *Ascaris lumbricoides*, *Trichuris trichuria* and *Hymenolepis nana)*, performed by Kato-Katz method [28,29], and the presence and intensity of *S. haematobium* was determined by the examination of the pellet resulting from 10ml centrifuged pre-treatment urine [28]. The intensity of *S. haematobium* infection was recorded as light, moderate

and heavy if 1–49, 50–499 and equal or more than 500 eggs per 10 ml of urine were observed, respectively, according to WHO recommendations [30]. We collected capillary blood samples for the diagnosis of uncomplicated malaria, performed by rapid diagnostic tests (RDTs) according to the manufacturer (SD BIOLINE Malaria Ag P.f/P.v, Standard Diagnostics, Inc). For the measurement of haemoglobin levels, we used the Hemocue System (HemoCue® 201 +, Angelholm, Sweden).

Adverse events data collection

We used a structured questionnaire to collect information on the adverse events (AEs) experienced by the children, performed to caretakers between 24 and 72 hours after treatment. When the caretaker was, absent and children had discernment to respond, the interview was performed with the children. Mild-to-moderate AEs were defined as undesirable experiences following drug administration, similarly to others, and severe AEs were defined as symptoms and signs due to administration drugs, which forced parents or caretaker to take their children to the health facility to be observed or hospitalized [31].

Statistical analysis

The collected data was first entered into the CISA database and then statistical analysis was conducted with SPSS version 23.0 computer software (IBM Corporation, New York, USA). Pearson's chi-square tests were used to compare the occurrence of AEs between the two surveys and for categorical variables. Alternatively, Fisher's exact test was used when any 2x2 contingency table cell expected a count below five.

We performed binary logistic model to identify possible independent predictors of AEs in the two surveys, using adjusted odds ratios (OR) and their 95% confidence interval (CI). The threshold for significant level was 0.05.

Ethics

All procedures performed in this study were in accordance with the standards of the 1964 Declaration of Helsinki and its later amendments. The Ethics Committee of the Angolan Ministry of Health approved the study protocol and all use of secondary data. Written informed consent was obtained and signed by a guardian, parent or a caretaker for each of the participants. A copy of the signed consent form, as well as contact information, was subsequently delivered to each participant. The Provincial health office, local leaders and parents were previously informed about the study in the area.

Results

A total of 605 children aged between 2 to 15 years (55.0% of males, 333/605) mean age 9.7 years ± 3.5, were subject to preventive chemotherapy with PZQ and ALB. Children with RDT positive for malaria were also treated with AL. At the baseline, of the 605 participating children, 548 took PZQ + ALB tablets while 57 took PZQ + ALB + AL. From those, 460 interviews were performed (76.0%, 460/605), responded mainly by the children themselves (75.0%) and guardians (25.0%). AEs were reported by 257 (55.9%, 257/460) children, 22 PSAC and 235 SAC. In this group of participants, 62.3% (160/257) were infected with either *S. haematobium* (100.0%, 160/160), STHs (20.6%, 33/160) and/or *Plasmodium falciparum* (19.4%, 31/160). On the other hand, 64.0% (130/203) of children, that had not experienced AEs, were also infected with those parasites (Fig 1). At the sixth month follow-up, 339 children included at the baseline, were surveyed for AEs after second round of medications (with PZQ+ALB or with PZQ

+ALB+AL), from which 184 (54.3%, 184/339) reported to have experienced at least one adverse event, 19.6% (36/184) PSAC and 80.4% (148/184) SAC, as shown in Fig 1.

No significant difference in the characteristics between participants and dropout children were observed at baseline. However, after the second round of treatment, a significantly lower proportion of PSAC (98.1% to 1.9%, $p<0.001$) and SAC (75.9% to 24.1%, $p<0.001$) were observed in the dropout group (Table 1).

In the first survey, headache (20.9%, 96/460), abdominal pain (18.5%, 85/460) and dizziness (15.7%, 72/460) were the three most frequently reported AEs. PSAC experienced mainly headache (18.6%), vomiting (14.3%) and abdominal pain (7.1%), whereas SAC, after headache (21.3%) and abdominal pain (20.5%) reported dizziness (18.2%). PSAC experienced significantly more vomiting than SAC (14.3% vs 6.7%, $p = 0.029$). SAC in turn experienced more abdominal pain (20.5% vs 7.1%, $p = 0.008$) and dizziness (18.2% vs 1.4%, $p<0.001$). Blood in stool and light sensitivity was only reported for SAC. After the second treatment, reports of abdominal pain, headache, dizziness and fatigue were also more frequent.

In this survey, PSAC reported significantly more fatigue (30.2% vs 15.4%, $p = 0.009$), blood in urine (20.8% *vs* 5.6%, $p<0.001$) and blood in stool (7.5% *vs* 1.0%, $p = 0.002$). Light sensitivity was not experienced by PSAC in both treatments, neither breathing difficulty after the second treatment (see Table 2).

Although, 2.3% (6/257) of children reporting AEs after the first treatment, and 1.6% (3/184) after the second treatment searched for medical attention in a nearby health facility but no admission notification was reported. Data on hospital care was not collected and therefore classification of the seriousness of AEs was not possible to perform.

Most children reported two simultaneous AEs followed by those reporting only one event (32.1% *vs* 31.5% in the first survey and 30.7% *vs* 29.2% in the second survey). There were also children who reported three or more simultaneous events. The most common single AEs were abdominal pain (37.9%, 22/58), headache (29.3%, 17/58) and fatigue (17.2%, 10/58) while double AEs were "abdominal pain + headache" (15.3%, 9/59), "fatigue + dizziness" (11.9%, 7/59) and "abdominal pain + fatigue" (6.8%, 4/59). Triple AEs were "abdominal pain + headache + dizziness" (12.1%, 4/33) and "abdominal pain + fatigue + dizziness" (6.1%, 2/33).

In the first survey, we observed that children with mixed infections had lower odds ratio to develop AEs than those with simple infections (adjusted OR = 0.14, p = 0.016 vs adjusted OR = 0.04, p = 0.011). Only the age group from 12 to 15 years old presented a significant OR of developing AEs (adjusted OR = 0.40, p = 0.040). All of these associations observed in the first survey lost their statistical significance after the second treatment. However, children with severe S. haematobium infection (adjusted OR = 2.72, p = 0.018) and children aged 9 to 11 years (adjusted OR = 2.01, p = 0.049) were significantly more probability to have AEs. (Table 3).

Discussion

In this study, 55.9% of the children who completed both surveys reported having experienced AEs after the first treatment with ALB, PZQ and/or AL and 54.3% after the second treatment. In general, the main AEs reported were abdominal pain, headache and dizziness, both after the first and after the second treatment, and only a low proportion of children searched for medical attention after both treatments (2.3% and 1.6%, respectively). The present study reported different proportions of AEs comparable to those found in other studies involving praziquantel and / or albendazole. However, there are variations that may occur due to the heterogeneous antecedents of the participating individuals, such as age, nutritional and immunological status, socioeconomic conditions, environmental exposure, prevalence and intensity of

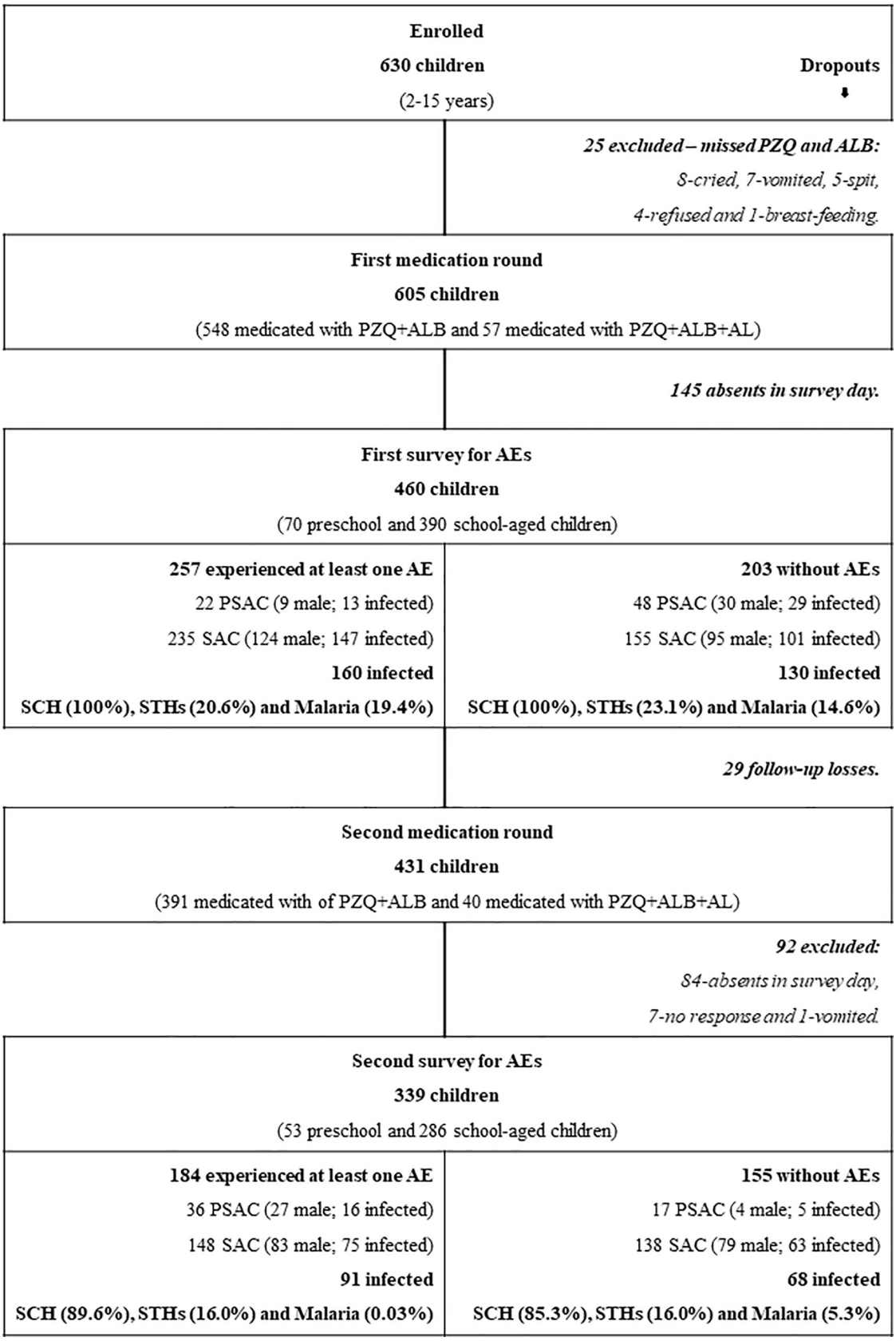
Enrolled
630 children
(2-15 years)
Dropouts
25 excluded – missed PZQ and ALB:
8-cried, 7-vomited, 5-spit,
4-refused and 1-breast-feeding.
First medication round
605 children
(548 medicated with PZQ+ALB and 57 medicated with PZQ+ALB+AL)
145 absents in survey day.
First survey for AEs
460 children
(70 preschool and 390 school-aged children)
257 experienced at least one AE
22 PSAC (9 male; 13 infected)
235 SAC (124 male; 147 infected)
160 infected
SCH (100%), STHs (20.6%) and Malaria (19.4%)
203 without AEs
48 PSAC (30 male; 29 infected)
155 SAC (95 male; 101 infected)
130 infected
SCH (100%), STHs (23.1%) and Malaria (14.6%)
29 follow-up losses.
Second medication round
431 children
(391 medicated with of PZQ+ALB and 40 medicated with PZQ+ALB+AL)
92 excluded:
84-absents in survey day,
7-no response and 1-vomited.
Second survey for AEs
339 children
(53 preschool and 286 school-aged children)
184 experienced at least one AE
36 PSAC (27 male; 16 infected)
148 SAC (83 male; 75 infected)
91 infected
SCH (89.6%), STHs (16.0%) and Malaria (0.03%)
155 without AEs
17 PSAC (4 male; 5 infected)
138 SAC (79 male; 63 infected)
68 infected
SCH (85.3%), STHs (16.0%) and Malaria (5.3%)

Fig 1. Study participants and dropouts. PSAC, preschool-aged children; SAC, school-aged children; SCH, schistosomiasis; SHTs, soil-transmitted helminths; AEs, adverse events; PZQ, praziquantel; ALB, albendazole; AL, Artemeter-Lumefantrine.

https://doi.org/10.1371/journal.pone.0229247.g001

infection, stage of parasite development, etc[13,18,20,21,31–37]. Zwang *et al* reviewed the efficacy and safety of PZQ (40mg/kg), and report that the main AEs experienced and their incidences are mainly abdominal pain (31.8%), muscle pain (29.2%), joint pain (20.2%), headache (13.6%), diarrhoea (12.9%), fatigue (9.6%), nausea (10.6%), dizziness (11.9%), vomiting (7.9%) and itching (9.8%) [18]. Additionally for ALB, there are reports of the occurrence of epigastric pain, dry mouth, fever and itching [18,21,32,38–40]. However, the occurrence of AEs are reported to be associated with the proportion of dying S. *haematobium* worms, i.e., with the pharmacologic effect of the drug on the parasite (for example; abdominal pain is reported to be associated with the deposition of dead worms in the mesenteric veins), they can also occur due to the natural course of disease [19,32,37,41,42].

Neumayr *et al* mentions that symptomatic acute schistosomiasis or treatment-induced reactions can manifest themselves with identical symptoms [32]. This group and others further discuss that the exposure to a high level of parasite antigens, caused by larval migration and maturation (of helminth larvae) or early oviposition in symptomatic acute schistosomiasis, can lead to an immune overreaction, resulting in symptoms that are similar to those reported as AEs to PZQ, but totally independent from treatment [19,32,43–45]. Although increasing the number of infections significantly reduced the chances of AE occurrence, we found that heavy S. haematobium infection was significantly associated with AEs occurrence, with odds ratio twice as high in individuals with this parasitic load in the second survey.Also, *H. nana* infections alone can cause headache, dizziness, abdominal pain and diarrhoea, *A. lumbricoides* can cause nausea, vomiting, diarrhoea and abdominal pain, *T. trichiura* can cause abdominal pain and diarrhoea, and *S. stercoralis* can cause erythema, itching, fever, abdominal pain and

Table 1. Characteristics of participants and dropouts in AEs survey.

	Baseline (n = 605)			6 months follow-up (n = 431)		
Characteristics	**Participants n = 460 (76.0%)**	**Excluded n = 145 (24.0%)**	***P value****	**Participants n = 339 (78.7%)**	**Excluded n = 92 (21.3%)**	***P value****
Age group						
PSAC[a]	70 (77.8)	20 (22.2)	0.674	53 (98.1)	1 (1.9)	<0.001
SAC[b]	390 (75.7)	125 (24.3)		286 (75.9)	91 (24.1)	
Gender						
Male	258 (77.5)	75 (22.5)	0.357	193 (80.1)	48 (19.9)	0.415
Female	202 (74.3)	70 (25.7)		146 (76.8)	44 (23.2)	
***S. haematobium* eggs**						
Positive	290 (76.1)	91 (23.9)	0.951	159 (81.5)	36 (18.5)	0.184
Negative	170 (75.9)	54 (24.1)		180 (76.3)	56 (23.7)	
Soil-transmitted helminths eggs						
Positive	156 (80.4)	38 (19.6)	0.058	58 (90.6)	6 (9.4)	0.603
Negative	205 (71.7)	81 (28.3)		163 (87.2)	24 (12.8)	
Missed examination	99 (79.2)	26 (20.8)		118 (65.6)	62 (34.4)	

* chi-square test

[a] Preschool-aged children

[b] School-aged children.

https://doi.org/10.1371/journal.pone.0229247.t001

Table 2. Frequency of reported AEs of children treated with PZQ and ALB in two medication rounds.

Adverse events	1st survey				2nd survey			
	PSAC[a] 70 (15%)	SAC[b] 390 (85%)	Total 460 (100%)	*p* value*	PSAC[a] 53 (16%)	SAC[b] 286 (84%)	Total 339 (100%)	*P* value*
Overall	**22 (31.4)**	**235 (60.3)**	**257 (55.9)**	**<0.001**	**36 (67.9)**	**148 (51.7)**	**184 (54.3)**	**0.043**
Abdominal pain	5 (7.1)	80 (20.5)	85 (18.5)	0.008	19 (35.8)	68 (23.8)	87 (25.7)	0.065
Headache	13 (18.6)	83 (21.3)	96 (20.9)	0.607	13 (24.5)	65 (22.7)	78 (23.0)	0.775
Dizziness	1 (1.4)	71(18.2)	72 (15.7)	<0.001	9 (17.0)	58 (20.3)	67 (19.8)	0.580
Fatigue	1 (1.4)	29 (7.4)	30 (6.5)	0.061	16 (30.2)	44 (15.4)	60 (17.7)	0.009
Vomiting	10 (14.3)	26 (6.7)	36 (7.8)	0.029	2 (3.8)	33 (11.5)	35 (10.3)	0.088
Blood in urine	1 (1.4)	29 (7.4)	30 (6.5)	0.061	11 (20.8)	16 (5.6)	27 (8.0)	<0.001
Fever	1 (1.4)	27 (6.9)	28 (6.1)	0.077	2 (3.8)	21 (7.3)	23 (6.8)	0.343
Itching	2 (2.9)	30 (7.7)	32 (7.0)	0.143	4 (7.5)	13 (4.5)	17 (5.0)	0.358
Diarrhoea	2 (2.9)	18 (4.6)	20 (4.3)	0.507	3 (5.7)	11 (3.8)	14 (4.1)	0.542
Light sensitivity	0 (0.0)	25 (6.4)	25 (5.4)	0.029	0 (0.0)	7 (2.4)	7 (2.1)	0.250
Joint pain	2 (2.9)	15 (3.8)	17 (3.7)	0.686	1 (1.9)	6 (2.1)	7 (2.1)	0.921
Blood in stool	0 (0.0)	4 (1.0)	4 (0.9)	0.395	4 (7.5)	3 (1.0)	7 (2.1)	0.002
Red skin	1 (1.4)	8 (2.1)	9 (2.0)	0.729	1 (1.9)	3 (1.0)	4 (1.2)	0.604
Breathing difficulty	2 (2.9)	11 (2.8)	13 2.8)	0.061	0 (0.0)	3 (1.0)	3 (0.9)	0.454

* chi-square test

[a] Preschool-aged children

[b] School-aged children.

https://doi.org/10.1371/journal.pone.0229247.t002

diarrhoea [35,38,46]. Thus, we postulate that children with mixed infections between schistosomiasis, STH and hymenolepiasis can be manifesting additive drug-unrelated AEs, overestimating the frequency of AEs reported here.

Despite that other authors have found no progression of AEs between treatment rounds, we found that after the second treatment the reports of abdominal pain, headache, dizziness and fatigue generally increased and the reports of joint pain and breathing difficulty generally decreased [20]. Additionally to that, experiencing 2 simultaneous AEs was slightly more frequent than experiencing only one event, and experiencing 3, 4 or 5 simultaneous events was also reported, despite of less frequent. Considering that the literature reports an association between AEs and the intensity of infection and anemia status, we found a statistically significant association between heavy infection and AEs [18,20,36]. Nevertheless, it should be considered that the administration of PZQ following a high-lipid or high-carbohydrate diets can increase its bioavailability (by a factor of 2.7 and 3.9) and in turn may alter the pharmacokinetic profile of the drug, possibly influencing the effect of the drug on the parasite and probably the frequency and type of AEs [18,19,33,41]. In this study children aged 9 to 15 years old, were at lower risk of experiencing AEs than younger children, however, it should be considered that this association lost their statistical significance after the second treatment and that the number of individuals within the PSAC group is small. Thus, these results should be interpreted carefully. Nevertheless, similar frequencies of AEs were observed by others between preschool and school children [21].

Regarding the 45% of "uninfected" children experiencing AEs in our study, in addition to the fact that these children may have AEs due to drug use only; we also considered the stages of infection undetected by the diagnostic technique used here [43,47]. The limited effect of PZQ on young forms of parasites and the progression of disease would still manifest signs and symptoms [40,43,47].

Table 3. Association between AEs and characteristics of participants in two AEs survey moments.

	1st survey			2nd survey		
Characteristics	**Total 257/339 (75.8%)**	**Adjusted 0R (95% CI)**	***P value***	**Total 184/339 (54.3%)**	**Adjusted OR (95% CI)**	***P value***
Gender						
Female	113/146 (77.4)	1	-	75/146 (51.4)	1	-
Male	144/193 (74.6)	0.96 (0.54–1.70)	0.904	109/193 (56.5)	1.18 (0.75–1.84)	0.463
Age group						
2–5 y	45/55 (81.8)	1		25/55 (45.5)	1	-
6–8 y	51/65 (78.5)	0.80 (0.30–2.09)	0.652	38/65 (58.5)	1.95 (0.91–4.18)	0.085
9–11 y	84/111 (75.7)	0.66 (0.28–1.59)	0.366	64/111 (57.7)	2.01 (1.00–4.05)	0.049
12–15 y	77/108 (71.3)	0.40 (0.16–0.95)	0.040	57/108 (52.8)	1.69 (0.84–3.39)	0.139
S. haematobium eggs						
Negative	97/130 (74.6)	1	-	102/195 (52.3)	1	-
Light (1-49eggs)	17/25 (68.0)	0.63 (0.23–1.71)	0.370	28/46 (60.9)	1.43 (0.73–2.80)	0.291
Moderate (50-499eggs)	75/100 (75.0)	1.13 (0.59–2.19)	0.700	29/62 (46.8)	0.73 (0.40–1.35)	0.324
Heavy (≥500eggs)	68/84 (81.0)	2.11 (0.76–3.26)	0.213	25/36 (69.4)	2.72 (1.18–6.24)	0.018
STHs Eggs						
Negative	205/251 (81.7)	1	-	159/298 (53.4)	1	-
Positive	52/88 (59.1)	2.11 (0.42–10.57)	0.361	25/41 (61.0)	0.43 (0.08–2.15)	0.310
Hymenolepis nana eggs						
Negative	241/313 (77.0)	1	-	177/328 (54.0)	1	-
Positive	16/26 (61.5)	1.77 (0.36–8.51)	0.475	7/11 (63.6)	1.95 (0.41–9.11)	0.395
Plasmodium parasites						
Negative	235/307 (76.5)	1	-	179/327 (54.7)	1	-
Positive	22/32 (68.8)	0.82 (0.34–1.94)	0.653	5/12 (41.7)	0.59 (0.17–2.00)	0.402
Number of infections						
Null	191/228 (83.8)	1	-	159/298 (53.4)	1	-
One	59/94 (62.8)	0.14 (0.30–0.69)	0.016	21/33 (63.6)	3.02 (0.58–15.69)	0.188
Two	7/17 (41.2)	0.04 (0.01–0.49)	0.011	4/8 (50.0)	1.67 (0.50–5.63)	0.402
Anaemia						
No	65/82 (79.3)	1	-	89/159 (56.0)	1	-
Yes	192/257 (74.7)	0.69 (0.36–1.34)	0.282	95/180 (52.8)	0.78 (0.50–1.24)	0.309

CI: confidence interval, OR: odds ratio, SHT: soil-transmitted helminths.

https://doi.org/10.1371/journal.pone.0229247.t003

Conclusions

This study adds evidence that chemotherapy for the control of schistosomiasis and soil-transmitted helminthiasis with PZQ and ALB is safe, although mild to moderate cases of AEs are expected. In these two surveys of AEs, we recorded 3.1% of children reporting medical attention due AEs after the medication. To assess the safety of co-administration of PZQ and ALB with artemeter-lumefantrine for positive cases of uncomplicated malaria in children, more standardized methodologies are needed to discriminate drug-related AEs from the clinical manifestations of the infections studied.

Supporting information

S1 File.
(DOCX)

S2 File.
(PDF)

Acknowledgments

We thank Calouste Gulbenkian Foundation for the project support and Health Research Centre of Angola (CISA, translated) for the technical assistance. We must not forget the valuable cooperation of the Provincial Health Department of Bengo, the National Program of Neglected Tropical Diseases and the Research Unit of the Porto Public Health Institute, in this project.

Author Contributions

Conceptualization: Manuel Lemos, Joao M. Pedro, Cláudia Fançony, Miguel Brito, Susana Vaz Nery, Carlos Pinto Sousa, Henrique Barros.

Data curation: Manuel Lemos, Sofia Moura.

Formal analysis: Manuel Lemos, Joao M. Pedro.

Funding acquisition: Manuel Lemos, Miguel Brito.

Investigation: Manuel Lemos, Cláudia Fançony, Sofia Moura, Miguel Brito.

Methodology: Manuel Lemos, Joao M. Pedro, Henrique Barros.

Project administration: Manuel Lemos, Miguel Brito, Susana Vaz Nery, Carlos Pinto Sousa, Henrique Barros.

Resources: Manuel Lemos, Sofia Moura, Miguel Brito.

Software: Manuel Lemos.

Supervision: Miguel Brito, Henrique Barros.

Validation: Miguel Brito, Susana Vaz Nery, Carlos Pinto Sousa, Henrique Barros.

Visualization: Susana Vaz Nery.

Writing – original draft: Manuel Lemos.

Writing – review & editing: Manuel Lemos, Joao M. Pedro, Cláudia Fançony, Sofia Moura, Miguel Brito, Susana Vaz Nery, Carlos Pinto Sousa, Henrique Barros.

References

1. Loukouri A, Méité A, Kouadio OK, Djè NN, Trayé-Bi G, Koudou BG, et al. Prevalence, Intensity of Soil-Transmitted Helminths, and Factors Associated with Infection: Importance in Control Program with Ivermectin and Albendazole in Eastern Côte d'Ivoire. J Trop Med. 2019 Mar 24. https://doi.org/10.1155/2019/7658594 PMID: 31019535
2. Aribodor DN, Bassey SA, Yoonuan T, Sam-Wobo SO, Aribodor OB, Ugwuanyi IK. Analysis of Schistosomiasis and soil-transmitted helminths mixed infections among pupils in Enugu State, Nigeria: Implications for control. Infect Dis Health. Infect Dis Health. 2019; 24(2): 98–106. https://doi.org/10.1016/j.idh.2018.12.003 PMID: 30648601
3. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014; 383(9936): 2253–64. https://doi.org/10.1016/S0140-6736(13)61949-2 PMID: 24698483
4. Idris OA, Wintola OA, Afolayan AJ. Helminthiases; prevalence, transmission, host-parasite interactions, resistance to common synthetic drugs and treatment. Heliyon. 2019; 5(1): e01161. https://doi.org/10.1016/j.heliyon.2019.e01161 PMID: 30775568
5. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Sachs SE, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med. 2006; 3(5): e102. https://doi.org/10.1371/journal.pmed.0030102 PMID: 16435908

6. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Invest. 2008; 118(4):1311–1321. https://doi.org/10.1172/JCI34261 PMID: 18382743

7. Direcção Nacional de Saúde Pública. Plano Estratégico Nacional de Doenças Tropicais Negligenciadas, 2017–2021 [Internet]. Ministério da Saúde da República de Angola. 2016. [Cited 2020 January 2020]. Available from: http://espen.afro.who.int/system/files/content/resources/ANGOLA_NTD_Master_Plan_2017_2021_0.pdf

8. Sousa-Figueiredo JC, Gamboa D, Pedro JM, Fançony C, Langa AJ, Magalhães RJS, et al. Epidemiology of malaria, schistosomiasis, geohelminths, anaemia and malnutrition in the context of a demographic surveillance system in northern Angola. PloS One. 2012; 7(4): e33189. https://doi.org/10.1371/journal.pone.0033189 PMID: 22493664

9. Soares Magalhães RJ, Langa A, Pedro JM, Sousa-Figueiredo JC, Clements ACA, Vaz Nery S. Role of malnutrition and parasite infections in the spatial variation in children's anaemia risk in northern Angola. Geospatial Health. 2013 May 1; 7(2): 341–54.

10. Reggi V, Daumerie D. (editors). Assuring safety of preventive chemotherapy interventions for the control of neglected tropical diseases [Internet]. World Health Organization.; 2011 [cited 2020 January 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44683/9789241502191_eng.pdf;jsessionid=5F644BA6A916665952DC286413295326?sequence=1

11. World Health Organization. Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions—a Manual for Health Professionals and Programme Managers. World Health Organization; 2006 [cited 2020 January 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43545/9241547103_eng.pdf?sequence=1

12. Horton J. Albendazole: a review of anthelmintic efficacy and safety in humans. Parasitology. 2000; 121 Suppl: S113–132.

13. Samuel F, Degarege A, Erko B. Efficacy and side effects of albendazole currently in use against Ascaris, Trichuris and hookworm among school children in Wondo Genet, southern Ethiopia. Parasitol Int. 2014 Apr 1; 63(2): 450–5. https://doi.org/10.1016/j.parint.2013.10.014 PMID: 24211489

14. Bada JL, Treviño B, Cabezos J. Convulsive seizures after treatment with praziquantel. Br Med J (Clin Res Ed). 1988 Feb 27; 296(6622): 646.

15. Stothard JR, Sousa-Figueiredo JC, Betson M, Bustinduy A, Reinhard-Rupp J. Schistosomiasis in African infants and preschool children: let them now be treated! Trends Parasitol. 2013 Apr; 29(4):197–205. https://doi.org/10.1016/j.pt.2013.02.001 PMID: 23465781

16. Odogwu SE, Ramamurthy NK, Kabatereine NB, Kazibwe F, Tukahebwa E, Webster JP, et al. Schistosoma mansoni in infants (aged < 3 years) along the Ugandan shoreline of Lake Victoria. Ann Trop Med Parasitol. 2006 Jun; 100(4): 315–26. https://doi.org/10.1179/136485906X105552 PMID: 16762112

17. Ekpo UF, Laja-Deile A, Oluwole AS, Sam-Wobo SO, Mafiana CF. Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria. Parasit Vectors. 2010 Jul 5; 3: 58. https://doi.org/10.1186/1756-3305-3-58 PMID: 20602792

18. Zwang J, Olliaro PL. Clinical efficacy and tolerability of praziquantel for intestinal and urinary schistosomiasis: a meta-analysis of comparative and non-comparative clinical trials. PLoS Negl Trop Dis. 2014; 8 (11):e3286. https://doi.org/10.1371/journal.pntd.0003286 PMID: 25412105

19. Olliaro PL, Vaillant MT, Belizario VJ, Lwambo NJS, Ouldabdallahi M, Pieri OS, et al. A multicentre randomized controlled trial of the efficacy and safety of single-dose praziquantel at 40 mg/kg vs. 60 mg/kg for treating intestinal schistosomiasis in the Philippines, Mauritania, Tanzania and Brazil. PLoS Negl Trop Dis. 2011 Jun; 5(6):e1165. https://doi.org/10.1371/journal.pntd.0001165 PMID: 21695161

20. Sousa-Figueiredo JC, Betson M, Atuhaire A, Arinaitwe M, Navaratnam AMD, Kabatereine NB, et al. Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. PLoS Negl Trop Dis. 2012; 6(10): e1864. https://doi.org/10.1371/journal.pntd.0001864 PMID: 23094120

21. Coulibaly JT, N'Gbesso YK, Knopp S, Keiser J, N'Goran EK, Utzinger J. Efficacy and safety of praziquantel in preschool-aged children in an area co-endemic for Schistosoma mansoni and S. haematobium. PLoS Negl Trop Dis. 2012; 6(12): e1917. https://doi.org/10.1371/journal.pntd.0001917 PMID: 23236526

22. Side Effects of Drugs Annual, Volume 36 - 1st Edition [Internet]. 2014 [cited 2020 January 10]. Available from: https://www.elsevier.com/books/side-effects-of-drugs-annual/ray/978-0-444-63407-8

23. Savioli L (editor). Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-age children. World Health Organization; 2011. [cited 2020 January 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44639/9789241501880_eng.pdf?sequence=1

24. Namwanje H, Kabatereine NB, Olsen A. The acceptability and safety of praziquantel alone and in combination with mebendazole in the treatment of Schistosoma mansoni and soil-transmitted helminthiasis

in children aged 1–4 years in Uganda. Parasitology. 2011 Oct; 138(12): 1586–92. https://doi.org/10.1017/S0031182011000138 PMID: 21349218

25. Stothard JR, Sousa-Figueiredo JC, Betson M, Green HK, Seto EYW, Garba A, et al. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. Parasitology. 2011 Oct; 138(12): 1593–606. https://doi.org/10.1017/S0031182011001235 PMID: 21861945

26. Costa MJ, Rosário E, Langa A, António G, Bendriss A, Nery SV. Setting up a demographic surveillance system in Northern Angola. Afr Popul Stud. 2012; 26(2).

27. Direcção Nacional de Saúde Pública. Directrizes e Normas de Conduta para o Diagnóstico e Tratamento da Malária [Internet]. Ministério da Saúde da República de Angola. 2014. [Cited 2020 January 2020]. Available from: https://www.severemalaria.org/sites/mmv-smo/files/content/attachments/2017-01-24/Angola%20Manual%20de%20Tratamento%20da%20Mala_ria%202014.pdf

28. World Health Organization. Basic laboratory methods in medical parasitology. Geneva: World Health Organization, 1991. «

29. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in Schistosomiasis mansoni. Rev Inst Med Trop Sao Paulo. 1972 Dec; 14(6): 397–400.

30. WHO Expert Committee on the Control of Schistosomiasis. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee [Internet]. World Health Organization. 2002. [Cited 2020 January 2020]. Available from: https://apps.who.int/iris/handle/10665/42588

31. Njenga SM, Ng'ang'a PM, Mwanje MT, Bendera FS, Bockarie MJ. A school-based cross-sectional survey of adverse events following co-administration of albendazole and praziquantel for preventive chemotherapy against urogenital schistosomiasis and soil-transmitted helminthiasis in Kwale County, Kenya. PloS One. 2014; 9(2): e88315. https://doi.org/10.1371/journal.pone.0088315 PMID: 24520365

32. Neumayr ALC, Tschirky B, Warren A, Hatz CFR, Blum JA. Acute Febrile Respiratory Reaction After Praziquantel Treatment During Asymptomatic Late Form of Acute Schistosomiasis. J Travel Med. 2012 Jul 1; 19(4): 264–7. https://doi.org/10.1111/j.1708-8305.2012.00626.x PMID: 22776392

33. Castro N, Medina R, Sotelo J, Jung H. Bioavailability of Praziquantel Increases with Concomitant Administration of Food. Antimicrob Agents Chemother. 2000 Oct 1; 44(10): 2903–4. https://doi.org/10.1128/aac.44.10.2903-2904.2000 PMID: 10991886

34. Muhumuza S, Olsen A, Katahoire A, Nuwaha F. Reduced uptake of mass treatment for schistosomiasis control in absence of food: beyond a randomized trial. BMC Infect Dis. 2015 Oct 14; 15: 423. https://doi.org/10.1186/s12879-015-1158-7 PMID: 26466681

35. Miyazato T, Furukawa T, Inoue T. Intestinal pathology associated with primary and secondary infections of Hymenolepis nana in mice. Japanese Journal of Parasitology. 1979: 28; 185–195.

36. Berhe N, Gundersen SG, Abebe F, Birrie H, Medhin G, Gemetchu T. Praziquantel side effects and efficacy related to Schistosoma mansoni egg loads and morbidity in primary school children in north-east Ethiopia. Acta Trop. 1999 Jan 15; 72(1): 53–63. https://doi.org/10.1016/s0001-706x(98)00084-9 PMID: 9924961

37. Odegaard JI, Hsieh MH. Immune responses to Schistosoma haematobium infection. Parasite Immunol. 2014; 36(9): 428–38. https://doi.org/10.1111/pim.12084 PMID: 25201406

38. Barroso H, Meliço-Silvestre A, Taveira N. (editors). Microbiologia Médica—Volume 2. Lisboa: LIDEL—Edições Técnicas; 2014.

39. Adoubryn KD, Kouadio-Yapo CG, Ouhon J, Aka NA, Bintto F, Assoumou A. [Intestinal parasites in children in Biankouma, Ivory Coast (mountaineous western region): efficacy and safety of praziquantel and albendazole]. Med Sante Trop. 2012; 22(2):170–6. https://doi.org/10.1684/mst.2012.0048 PMID: 23107664

40. Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois J-P, et al. Efficacy of praziquantel during the incubation and invasive phase of schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg. 2006 May; 74(5): 814–8. PMID: 16687686

41. Metwally A, Bennett J, Botros S, Ebeid F, el attar G el D. Impact of drug dosage and brand on bioavailability and efficacy of praziquantel. Pharmacol Res. 1995 Jan; 31(1): 53–9. https://doi.org/10.1016/1043-6618(95)80048-4 PMID: 7784306

42. N'Goran EK, Gnaka HN, Tanner M, Utzinger J. Efficacy and side-effects of two praziquantel treatments against Schistosoma haematobium infection, among schoolchildren from Côte d'Ivoire. Ann Trop Med Parasitol. 2003 Jan; 97(1): 37–51. https://doi.org/10.1179/000349803125002553 PMID: 12662421

43. Jauréguiberry S, Caumes E. Clinical Management of Acute Schistosomiasis: Still Challenging! J Travel Med. 2011 Nov 1; 18(6): 365–6. https://doi.org/10.1111/j.1708-8305.2011.00561.x PMID: 22017710

44. Raso G, N'Goran EK, Toty A, Luginbühl A, Adjoua CA, Tian-Bi NT, et al. Efficacy and side effects of praziquantel against Schistosoma mansoni in a community of western Côte d'Ivoire. Trans R Soc Trop Med Hyg. 2004 Jan 1; 98(1): 18–27. https://doi.org/10.1016/s0035-9203(03)00003-8 PMID: 14702835

45. Mahmoud AAF (editor). Schistosomiasis. London: River Edge, NJ: Imperial College Press; 2001.

46. Tomita S. Clinical Observations on Patients infested with Hymenolepis nana, with Special Reference to Changes In their Blood Pictures. J Med Assoc Formosa. 1937; 36(5): 386.

47. Chunge CN, Chunge RN, Masinde MS, Atinga JN. An outbreak of acute schistosomiasis following a church retreat to Mwanza, Tanzania, 2008. J Travel Med. 2011; 18(6): 408–410. https://doi.org/10.1111/j.1708-8305.2011.00558.x PMID: 22017717