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The efficacy of praziquantel in school children infected with urogenital schistosomiasis in sub-Saharan Africa: a systematic review from 2005 to 2020

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Abstract: Praziquantel is the only drug recommended by the World Health Organization to treat schistosomiasis, and this raises concerns about possible resistance to the drug. The aim of this review is to assess the efficacy of praziquantel in the treatment of schistosomiasis in school-age children in sub-Saharan Africa. **Methods**: This review was carried out using PubMed and Google Scholar. The review included field studies investigating the efficacy of praziquantel-based treatment of *Schistosoma haematobium* in school-aged children at the community and/or school level from 2005 to 2020 in sub-Saharan Africa. Excluded studies were those that did not meet the inclusion criteria. **Results**: Of a total of eleven articles included, Nigeria had four articles (4/11; 36.4%), followed by Senegal and Tanzania with two articles each (2/11; 18.2%), and Mali, South Africa and Sudan with one article each (1/11; 9.1%). Praziquantel showed high cure rates and reduced prevalence in children up to 12 weeks after treatment. Further results showed that seven weeks after praziquantel administration, treated children continued to excrete eggs in the urine, none of which were viable. Double-dose praziquantel at 40 mg/kg administered over a four-week interval was more effective than a single dose of 40 mg/kg. **Conclusion:** Treatment with two doses per year in high-transmission areas and once a year in low-transmission areas could minimize the risk of reinfection.

Keywords: praziquantel; efficacy; schistosomiasis; school-age children; sub-Saharan Africa

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Introduction

Schistosomiasis is a public health problem worldwide [1–3]. It is the second most deadly parasitic cause after malaria, endemic in 74 countries. Approximately 261 million people are infected worldwide, and nearly 800 million people are exposed to the disease [3,4]. Sub-Saharan Africa (SSA) is the most affected region, accounting for 90% of infections [5,6]. It is considered a disease of poverty, and unequally affects the less wealthy [7,8]. The *Schistosoma haematobium* and *Schistosoma mansoni* species are responsible for the burden of schistosomiasis, although the *Schistosoma haematobium* species *(S. haematobium)* is more widespread in the sub-Saharan region [9]. Infection can occur when humans come into contact with schistosome larvae in water, which are cercariae released by intermediate snail hosts [10,11]. The supply of safe drinking water and improved hygiene and sanitation, combined with preventive chemotherapy using praziquantel, are considered the basic strategies for reducing the burden of schistosomiasis [11]. Environmental concerns and the high costs associated with intermediate host control hinder the realization of a successful global schistosomiasis control strategy [12]. Good progress in reducing schistosomiasis morbidity and mortality has been made in Brazil, Cambodia, Egypt, China and the Philippines [13]. Since 1984, the World Health Organization (WHO) has approved a drug treatment, praziquantel (PZQ), a broad-spectrum anthelmintic aimed at reducing the morbidity of *Schistosoma* infection [3]. A standard single oral dose of 40 mg/kg bodyweight remains the drug recommended by the World Health Organization for community- and school-based mass treatment (CT) [10,11]. Every year, endemic African countries receive praziquantel to treat and prevent schistosomiasis in millions of school-age children [14,15]. Compliance with the treatment is difficult, particularly among people living in disadvantaged socio-economic areas due to fear of adverse effects and the apparent absence of disease symptoms, and even when symptoms do appear, they are often stigmatized [16,17] or considered a normal sign of puberty, not requiring treatment [18,19]. Tremendous efforts have been made to eliminate schistosomiasis over the last decade by the World Health Organization, having set the goal of interrupting transmission in endemic African countries by 2030 [20]. Government agencies in several countries have given priority to controlling neglected tropical diseases (NTDs) by exploiting the lifestyle of intermediate hosts throughout their cycle, such as implementing snail control and improving sanitation and access to safe, clean water [21,22]. School-age children are the main targets for control, as they are considered the most at risk of infection. They are most likely to take part in daily activities such as fishing, rice growing and swimming, which expose them to a higher risk of infection compared to other age groups [23]. Protective immune responses against schistosomes develop slowly, while children in schistosomiasis-endemic areas are generally susceptible to reinfection after treatment for schistosomiasis [23]. Despite annual or two-yearly treatments, it has been reported that reinfection occurs in endemic areas in less than 12 months in several treated children [24]. This highlights the need for further investigations into the efficacy of praziquantel against *Schistosoma haematobium* in endemic areas of sub-Saharan Africa. In Mali, few studies have been carried out on reinfection after treatment, so it was necessary to review articles published in the sub-Saharan African region between 2005 and 2020 that address the efficacy of praziquantel in the treatment of schistosomiasis in school-age children, with a view to informing decision-makers.

Methodology

Research plan for the systematic review

This systematic review was carried out using accessible databases, mainly from PubMed and Google scholar between 2005 and 2020. However, we did not find any results through Joanna Briggs. The selection was made using the following terms: “Efficacy of praziquantel” AND “Schistosoma haematobium” AND “prevalence” AND “intensity” AND “School-age children” AND “Sub-Saharan Africa”. To identify articles, titles and abstracts were used to select relevant articles. Relevant abstracts were then assessed for inclusion in the list of full-text articles. All full-text articles were saved in Excel and Zotero (a free reference management software for managing bibliographic data and associated research documents).

This review includes research articles published over a 15-year period from 2005 to 2020. An independent reviewer (HM) examined the full text of the included publications for a qualitative review and to extract information on the efficacy of praziquantel in the treatment of schistosomiasis in school-age children.

Inclusion/non-inclusion criteria

- **Inclusion criteria:**
  - All studies investigating the efficacy of praziquantel-based mass treatment against *Schistosoma haematobium* in school-aged children in sub-Saharan Africa;
  - All articles published in English and French between 2005 and 2020;
  - All community or school-based studies.
- **Non-inclusion criteria:**
  - All studies on the side effects of praziquantel-based treatment in school-age children in sub-Saharan Africa;
  - All articles published before 2005 and after 2020;
  - All studies investigating the efficacy of praziquantel in combination with other drugs;
  - All studies investigating the efficacy of praziquantel in the context of coinfection with schistosomiasis and other parasites;
  - All studies in which the study population included adults;
  - All experimental laboratory studies on the efficacy of praziquantel.

Results

As part of the article search, Google Scholar provided six hundred and thirty-three (633) records. We obtained 13 articles that were registered from the PubMed database. Overall, we registered a total of 620 articles after removing duplicates (Figure 1). Of the 620 articles, 609 were deemed ineligible according to our inclusion criteria. We had a total of 11 articles eligible for review, including field studies investigating the efficacy of praziquantel-based treatment against *Schistosoma haematobium* in school-aged children in sub-Saharan African countries at the community or school level from 2005 to 2020. Articles excluded were those that included adults, those published before 2005 and after 2020, studies on the efficacy of praziquantel in combination with other drugs and studies on the side effects of the treatment.

Selected studies by country

Out of a total of eleven articles reviewed, Nigeria was the country with the most studies (4/11 = 36.4%) [25–28], followed by Senegal and Tanzania with two articles each (2/11 = 18.2%) [29–32]. Countries such as Mali, South Africa and Sudan each produced one article (1/11 = 9.1%) [33–35] (Table 1).

Table 1: A list of studies on the efficacy of praziquantel in the control of urogenital schistosomiasis by country between 2005 and 2020.

Authors and References	Year	Country	Title	Study Population	Study Type
Adewale et al. [25]	2018	Nigeria	Impact of Single Dose Praziquantel Treatment on *Schistosoma haematobium* Infection among School Children in an Endemic Nigerian Community	School-age children	Interventional
Houmsou et al. [26]	2018	Nigeria	High Efficacy of Praziquantel in *Schistosoma haematobium*-Infected Children in Taraba State, Northeast Nigeria: A follow-up study	School-age children	Interventional
Ojurongbe et al. [27]	2014	Nigeria	Efficacy of praziquantel in the treatment of *Schistosoma haematobium* infection among school-age children in rural communities of Abeokuta, Nigeria	School-age children	Interventional
Onifade et al. [28]	2018	Nigeria	Prevalence of urinary schistosomiasis and efficacy of praziquantel; a case study of school pupils in Oke-Igbo, Ondo State, Nigeria	School-age children	Study cases
Senghor et al. [29]	2015	Senegal	Efficacy of praziquantel against urinary schistosomiasis and reinfection in Senegalese school children where there is a single well-defined transmission period	School-age children	Cohort and longitudinal

Leye et al. [30]	2013	Senegal	Effet du traitement de masse avec le praziquantel sur la bilharziose urinaire en milieu scolaire chez les enfants âgés de 7 à 14 ans dans le district sanitaire de Linguère (Sénégal)	School-age children	Cross-sectional
Chaula et al. [31]	2014	Tanzania	Impact of praziquantel mass drug administration campaign on prevalence and intensity of *Schistosoma haematobium* among school children in Bahi district, Tanzania	School-age children	Cross-sectional
Guidi et al. [32]	2010	Tanzania	Praziquantel efficacy and long-term appraisal of schistosomiasis control in Pemba Island	School-age children	Cohort
Ahmed et al. [33]	2012	Sudan	*Schistosoma haematobium* infections among school children in central Sudan one year after treatment with praziquantel	School-age children	Longitudinal
Dabo et al. [34]	2015	Mali	Impact of Mass Praziquantel Administration for Controlling *Schistosoma haematobium* Infection in School children from Bamako, Mali	School-age children	Cross-sectional
Kabuyaya et al. [35]	2017	South Africa	Efficacy of praziquantel on *Schistosoma haematobium* and re-infection rates among school-going children in the Ndumo area of uMkhanyakude district, KwaZulu-Natal, South Africa	School-age children	Cohort

Efficacy of praziquantel against *S. haematobium*

This review showed high cure rates and a possible reduction in the prevalence and intensity of *S. haematobium* in children at four, eight and twelve weeks after treatment with PZQ [23,28–30]. The results showed that several treated children continued to expel eggs in the urine up to seven weeks after praziquantel administration but none of these eggs were viable [32]. There was a difference between cure rates and infection intensities in urogenital schistosomiasis [36,37]. (Table 2).

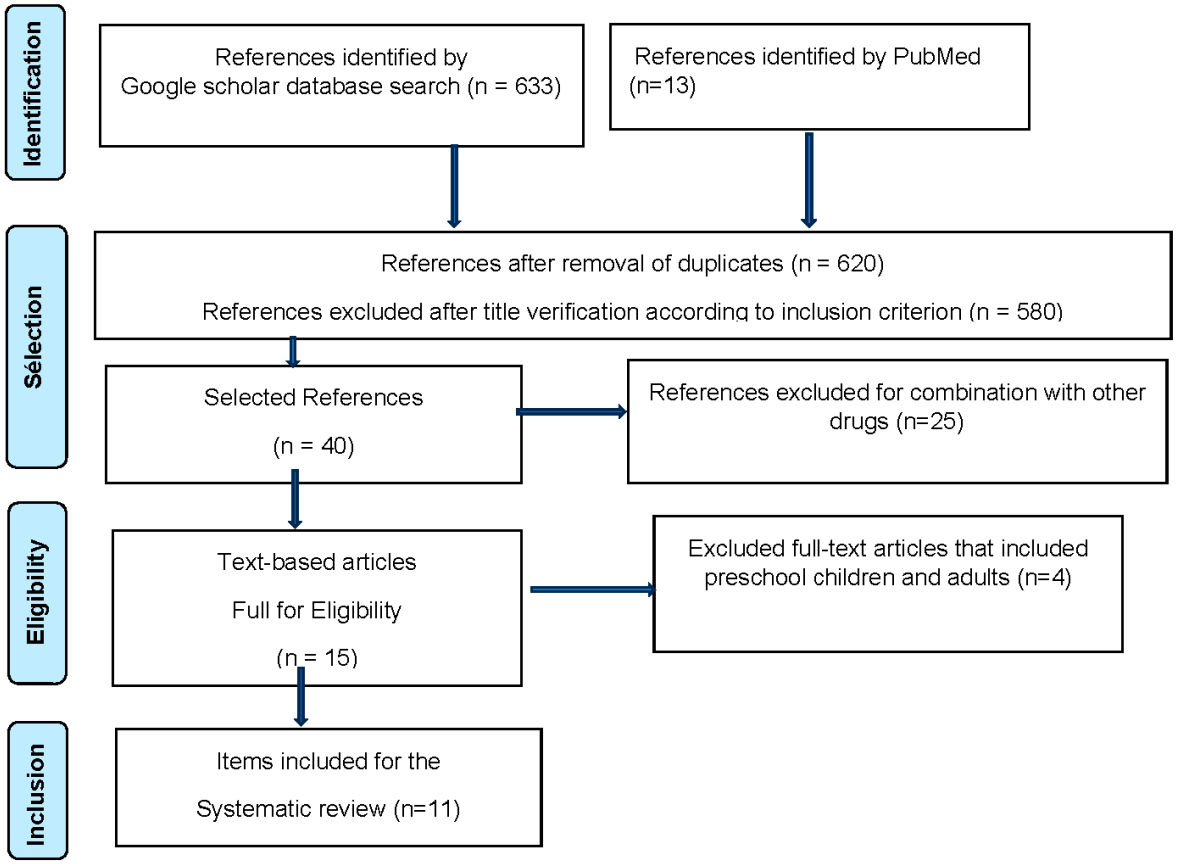

Figure 1: Flow diagram of articles included in systematic review.

Praziquantel treatment failures and reinfection rates

In the course of this review, cases of failure and reinfection were reported after treatment with praziquantel. However, studies that used only a single dose for treatment had high rates of reinfection after 6 to 12 months [25,29,32]. Nevertheless, only one case of failure was confirmed after an egg viability test [35].

Therapeutic dosages used to assess the efficacy of praziquantel against *S. haematobium*

Previous studies have shown that the administration of a single dose of praziquantel significantly reduces the prevalence and intensity of transmission of *Schistosoma haematobium* [11,28]. In this review, a single dose of 40 mg/kg body weight of praziquantel showed a significant reduction in the prevalence and intensity of infection in the third and fourth month and after one year in study populations in some countries [11,19,21,23,28]. On the other hand, a satisfactory reduction in the prevalence of infection was observed after a few weeks of treatment in countries that chose to use a second dose of treatment with an interval of four weeks in relation to the first treatment [20,21,29] (Table 2).

Table 2: Classification of studies on impact of praziquantel against *Schistosoma haematobium* between 2005 and 2020 in sub-Saharan Africa

Authors and references	Year	Title	Objectives	Age Group	Dose in mg	Sample size	Prevalence	Mean Egg Count	Conclusion
Adewale et al. [25]	2018	Impact of Single Dose Praziquantel Treatment on *Schistosoma haematobium* Infection among School Children in an Endemic Nigerian Community	To assess the impact of single-dose praziquantel treatment on *Schistosoma haematobium* infection in school children in an endemic community in southwest Nigeria.	5 to 18	40	434	The prevalence was 24.9% at pre-treatment. Interestingly, the prevalence of infection rose from 2.1% at 6 months to 7.7% at 12 months post-treatment.	Six and twelve months after treatment, the mean number of eggs were reduced by 74.4% and 86.4%, respectively. Moreover, the mean egg count was reduced to 0.27 at 12 months compared with 1.98 six months after treatment.	The resurgence of the prevalence rate between 6 and 12 months after praziquantel treatment is reported here, and the need for follow-up treatment in endemic areas to have an adequate impact on schistosomiasis control is discussed.
Houmsou et al. [26]	2018	High Efficacy of Praziquantel in *Schistosoma haematobium*-Infected Children in Taraba State, Northeast Nigeria: A follow-up study	To evaluate the efficacy of praziquantel in reducing the prevalence of urinary schistosomiasis, the parasite load and the morbidity rate in a previously reported sample of children infected with *Schistosoma haematobium*.	6 to 15	40	675	Four weeks after treatment, the overall cure rate was 98.1%. In children with a low and high parasite load at baseline, egg reduction rates were 100% and 96.5%, respectively. One year after treatment, 272 infected children (40.3%) were reassessed; of these, 51 children (18.8%) were reinfected.	-	A moderate rate of reinfection was noted.

Ojurongbe et al. [27]	2014	Efficacy of praziquantel in the treatment of *Schistosoma haematobium* infection among school-age children in rural communities of Abeokuta, Nigeria	This study was conducted to assess the efficacy of taking two doses of oral praziquantel for the treatment of school children in rural communities in Nigeria.	4 to 15	40	350	At four, eight and twelve weeks after treatment, the reduction rate was 57.1%, 77.6% and 100%, respectively. After the second cycle of treatment, the cure rate at eight and twelve weeks was 85.3% and 100%, respectively.	-	This study demonstrated the efficacy of taking two oral doses of PZQ for the treatment of urinary schistosomiasis in school children in Nigeria.
Onifade et al. [28]	2018	Prevalence of urinary schistosomiasis and efficacy of praziquantel; a case study of school pupils in Oke-Igbo, Ondo State, Nigeria	To assess the prevalence of urinary schistosomiasis and the efficacy of praziquantel in a case study of school children in Oke-Igbo, Ondo State, Nigeria.	4 to 15	40	528	Of the 528 pupils, 105 (19.9%) were infected, while 37 (7.0%) had visible hematuria. At 3 months after treatment, seven (6.7%) pupils were still positive after re-screening, with hematuria in four (3.8%) pupils.	Praziquantel administered as a single oral dose at 40 mg/kg body weight showed a 77.72% reduction in the geometric mean number of eggs.	Control of the disease in Ondo State is essentially focused on chemotherapy, so the rate of reinfection after parasitological cure is still a major concern.
Senghor et al. [29]	2015	Efficacy of praziquantel against urinary schistosomiasis and reinfection in Senegalese school children where there is a single well-defined transmission period	The aim of this study was to i) determine the current prevalence of *S. haematobium* in children in Niakhar, ii) evaluate the efficacy of a dose of PZQ of 40 mg/kg of body weight against *S. haematobium* and iii) monitor reinfection.	5 to 15	40	329	A single dose of PZQ significantly reduced the prevalence of *S. haematobium* infection from 73.2% to 4.6%. The overall prevalence at this time was 13.8%, which was significantly lower than the prevalence at baseline (73.2%).	A single dose of PZQ significantly reduced the geometric mean intensity of infection from 356.1 to 43.3 eggs/10ml of urine.	The Niakhar study area remains a hot spot for urinary schistosomiasis in Senegal, with differences in transmission between villages.

Leye et al. [30]	2013	Effect of mass treatment with praziquantel on urinary bilharziasis in school children aged 7 to 14 years in the health district of Linguère (Senegal)	To determine the effect of mass treatment with praziquantel against urinary bilharziasis in school children aged 7–14 years in the health district of Linguère, Senegal.	7 to 14	40	360	An overall prevalence of 24.4%. Among the pupils who had received praziquantel during the mass treatment, 28% were infected with bilharzia. Among those who had not received praziquantel, the prevalence was 7.8%.	-	In addition to chemoprophylaxis, it is important to carry out awareness-raising activities involving all of the players concerned, especially the local population.
Chaula et al. [31]	2014	Impact of praziquantel mass drug administration campaign on prevalence and intensity of *Schistosoma haematobium* among school children in Bahi district, Tanzania	To assess the impact of the two rounds of MT on the prevalence and intensity of *Schistosoma haematobium* and the impact of the MT campaigns on knowledge of urinary schistosomiasis, the use of drinking water and contact with potentially dangerous watercourses.	8 to 19	40	488	The prevalence of *Schistosoma haematobium* fell significantly by 50.0%, from 26% in 2011 to 15% in 2012 (p = 0.000). The prevalence of *S. haematobium* was significantly lower in school children participating in the CT (3.1%) than in the non-participating school children (28.5%) (p = 0.000).	-	In conclusion, although the CT significantly reduced the prevalence of *S. haematobium*, participation was below 50.0% and below the target of 75.0% set as recommended by the World Health Assembly Resolution. It was 54.19 for 2010.
Guidi et al. [32]	2010	Praziquantel efficacy and long-term appraisal of schistosomiasis control in Pemba Island	To conduct a retrospective analysis of the performance of schistosomiasis control programs.	6 to 18	40	1531	Although 5% of treated children continued to excrete eggs in the urine until the seventh week after praziquantel administration, none of these eggs were viable.	-	An overall retrospective analysis of schistosomiasis control activities on the island of Pemba revealed that mass drug administration is clearly effective in reducing the prevalence of infection.

Ahmed et al. [33]	2012	*Schistosoma haematobium* infections among school children in central Sudan one year after treatment with praziquantel	To study the prevalence and intensity of *S. haematobium* infection one year after praziquantel treatment in school children in al Salamania, central Sudan.	6 to 15	40	562	A single dose of praziquantel significantly reduced the prevalence of *S. haematobium* infection by 83.3%.	The geometric mean intensity of infection of positive individuals was 17.0% one year after treatment.	There was a significant reduction in *S. haematobium* infection one year after treatment with PZQ.
Dabo et al. [34]	2015	Impact of Mass Praziquantel Administration for Controlling *Schistosoma haematobium* Infection in School children from Bamako, Mali	To assess the impact of mass administration of praziquantel on the prevalence and intensity of *Schistosoma haematobium* in school children in Bamako between 2011 and 2014.	8 to 15	40	672	The prevalence of infection was 16.2% (109/672) (95% CI; 16.1–16.3). Despite the global increase in infection ranging from 14.7% in 2011 to 16.2% in 2014, the infection rates were comparable (p = 0.46).	The geometric mean egg count was 0.1639.	The findings show a mitigated positive effect of the MPA strategy on S. haematobium prevalence in the urban area of Bamako.
Kabuyaya et al. [35]	2017	Efficacy of praziquantel on *Schistosoma haematobium* and re-infection rates among school-going children in the Ndumo area of uMkhanyakude district, KwaZulu-Natal, South Africa	To evaluate the efficacy of PZQ and determine the rate of reinfection and the incidence of *Schistosoma haematobium* infection in school children in the Ndumo region, KwaZulu-Natal.	10 to 15	40	320	At 20 and 28 weeks after treatment, reinfection rates were 8.03% and 8.00%, respectively, giving an overall rate of 8.1%. An incidence rate of 4.1% was observed 28 weeks after the initial screening.	-	The study showed a high cure rate, while the egg reduction rate was low, suggesting a reduced efficacy of PZQ. Reinfection rates at 20 and 28 weeks post-treatment were low. The study also showed a low incidence rate for the 28-week period.

Discussion

Our review was based on the efficacy of praziquantel in school-aged children infected with urogenital schistosomiasis in sub-Saharan Africa from 2005 to 2020. Praziquantel has been shown to be effective against *Schistosoma haematobium* at a single standard dose of 40 mg/kg body weight [9,27,33,35,38]. Thus, to eliminate the infection, the need for a further dose in some countries with low cure rates has been reported [25,27,29,35]. In fact, praziquantel is ineffective against juvenile schistosomes, which can then mature and release eggs [35,39]. After treatment with praziquantel, infection may persist due to the activity of children in contact with contaminated water [26,28]. Reinfection is possible when children, after successful treatment with praziquantel, resume activities involving contact with cercarial-infested water, hence the need for health education to reduce water contact [26,29]. In our review, one case of treatment failure was reported in children with a high intensity of infection [27,33,35]. This was due to poor absorption of the drug rather than parasite resistance, which has been associated with the ineffectiveness of praziquantel [40,41]. However, constant monitoring of praziquantel efficacy is important while awaiting the discovery and development of new drugs [27,32,35,40]. It would also be advantageous to consider taking therapeutic doses of praziquantel at different time intervals as it has been reported that a double dose of 40 mg/kg administered over a four-week interval is more effective than a single treatment in endemic areas [27,36]. Thus, in studies where the dose was repeated over a four-week interval, few treated cases continued to release viable eggs [42]. However, the mass distribution of praziquantel-based drugs raises concerns about possible resistance [9,43]. Follow-up after mass distribution is necessary in most cases, as praziquantel is the only drug for schistosomiasis at 40 mg/kg body weight [44,45]. Since a single dose does not completely eliminate the parasite [25,27,29,35]. It is important to conduct educational awareness campaigns to warn residents of the risk factors associated with schistosomiasis reinfections [9,46]. In addition, supplying drinking water by installing new boreholes or reactivating old boreholes or wells in these communities could reduce host–vector contact [5,26,35]. This supply of drinking water could also reduce the incidence of frequent schistosomiasis infections [5,26,35]. In the context of drug administration, papers that have repeatedly used the standard dose of 40mg/kg have shown efficacy in reducing the intensity of infection after the second dose [26,27,35]. The reasons for administering the second dose were to target immature worms not eliminated by the first treatment and to do so between eight and twenty-eight weeks after the initial treatment [26,27,35]. Infection may persist after treatment due to the reduced sensitivity of immature parasites to the drug. Thus, they may develop tolerance or resistance over time [47,48]. Non-viable eggs may be present for months in the urine of patients treated for *Schistosoma haematobium* and will falsely limit the results of egg reduction and cure rates [49]. The efficacy of mass treatment has been shown to reduce the prevalence of infection, but soon after drug distribution is interrupted, prevalence rapidly returns to pre-intervention levels [32]. This has prompted researchers to conduct trials with a single dose of 60 mg/kg body weight to prevent failure/resistance [50]. Investigators who have conducted comparative studies of praziquantel with the standard dose of 40 mg/kg versus the 60 mg/kg body weight split dose have reported divergent results on the efficacy of schistosomiasis treatment [51,52].

In addition, several authors have reported that the efficacy of praziquantel at a single dose of 60mg/kg body weight is similar to that of the 40 mg/kg body weight dose [44,51,53]. A dose higher than 40 mg/kg of body weight does not therefore provide any added value in the treatment of *Schistosoma haematobium* infection [43,45,51]. Today, the fight against schistosomiasis is still based on the large-scale treatment of at-risk population groups, access to drinking water, improved sanitation, hygiene education, behavioral change, gastropod control and environmental management [22]. The new Roadmap for Neglected Tropical Diseases 2021-2030, adopted by the World Health Assembly, has set the global objective of eliminating schistosomiasis as a public health problem in all endemic countries and interrupting transmission (the absence of infection in humans)

in certain countries [54]. The WHO focuses its control strategy on reducing morbidity through regular, targeted praziquantel treatment as part of the large-scale treatment (chemoprophylaxis) of at-risk populations [9]. All at-risk groups receive regular treatment. In countries where transmission is low, the aim should be to interrupt transmission. Access to gray literature and the similarity of the content of the search databases were limitations of this review.

Conclusion and recommendations

This review has shown that praziquantel is effective against *Schistosoma haematobium*. It also revealed that praziquantel administered at a standard repeated dose of 40 mg/kg body weight over a four-week interval is more effective than the standard single dose of 40 mg/kg body weight. However, cases of therapeutic failure and reinfection have been reported. It is therefore important to monitor the efficacy of praziquantel while awaiting the discovery and development of new drugs against this parasite. However, proximity to watercourses and participation in water-related activities such as fishing and farming are important factors predisposing children to reinfection after treatment. Treatment with two doses per year in areas of high transmission and once a year in areas of low transmission could minimize the risk of reinfection in children, in addition to other preventive measures.

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