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Schistosomiasis in Nigeria: Gleaning from the past to improve current efforts towards control

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ABSTRACT

The effort to control schistosomiasis in Nigeria has been scaled up the past few years. Schistosomiasis affects all age groups, however, school children are at the highest risk of the disease. In the past years, global partners in schistosomiasis control have renewed their commitments. Many countries including few in Africa are working towards eliminating the disease. In Nigeria, the transmission of schistosomiasis is still active. This poses a serious health challenge as morbidity builds up in infected individuals. Mass drug administration (MDA) has helped to reduce morbidity but it is not adequate to abate transmission in many areas of the country. The integration of other aspects of control will provide a more sustainable result. This review attempted to discuss schistosomiasis transmission patterns in Nigeria in different eras. We identified some pitfalls in efforts towards the control of schistosomiasis in Nigeria. We recommended research priority in areas of neglect and advocated for integrated control.

1. Introduction

Schistosomiasis is a water-borne parasitic disease and it is endemic in the poorest regions of sub-Saharan African countries. Schistosomiasis is caused by five major species of schistosome. *Schistosoma mansoni*, *S. intercalatum*, *S. japonicum*, and *S. mekongi* cause intestinal schistosomiasis while *S. haematobium* causes urogenital morbidities. *S. mansoni* and *S. haematobium* are the predominant species in sub-Saharan African countries. Transmission occurs when an infected person passes urine or faeces into water bodies. This is common in resource-limited rural, peri-urban or urban areas. The eggs passed into the water develop into miracidia which are released from the eggs and swim to locate specific freshwater snail hosts. They develop in the snails into sporocysts which in turn develop into the infective stage of the parasite called cercariae. Human acquires the infection during contact with cercariae infested freshwater bodies [1].

Schistosomiasis cases occur in about 258 million people worldwide [2]. Sub-Saharan African countries with about 90% of the world's total cases are the most affected regions [3]. In Nigeria, 20 million people need to be treated annually, thus, it is the most affected country in the world [4]. School-based deworming with Praziquantel (PZQ) is the main intervention for schistosomiasis in Nigeria. PZQ became the drug of choice for mass drug administration (MDA) because of its efficacy against all the species of schistosomes. It is cost-effective, available, safe, and only requires minimal training of non-medical personnel [4].

In 2001, the World Health Assembly (WHA) prioritised schistosomiasis on the international health agenda. The member states passed a resolution for the control of the disease in endemic areas. The countries were urged to meet a target of regular treatment of "at least 75% and up to 100% of all school-aged children at risk of morbidity by 2010" [5]. In Nigeria, during this period, the national policy on disease control did not favour schistosomiasis. This resulted in a very low PZQ coverage index in schistosomiasis endemic areas [3]. In January 2012, stakeholders and partners, including, the government of NTDs endemic countries, donors, a coalition of global health institutions, pharmaceutical companies, and non-governmental organisations endorsed the London Declaration [6].

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Since 2012, the Nigerian government has given more attention to NTDs' control. The country has recorded a gradual increase in the PZQ coverage index among people at high risk of schistosomiasis.

The World Health Organisation (WHO) set a target of schistosomiasis morbidity reduction of <5% prevalence in children aged 5–14 years by 2020 for endemic countries [7]. Despite a decade of efforts to mitigate the disease transmission, Nigeria is far from achieving the WHO's target. The Nigeria experience calls for the adoption of a holistic approach towards control of schistosomiasis. The integrated approach towards control of schistosomiasis could include intervention informed by appropriate and reliable mapping of the disease, snail control, provision of safe water, and evidence-based decision making in policy development.

This review attempted to discuss schistosomiasis morbidity patterns in different eras. We sought to know how various WHA Resolutions and the 2012 London Declaration have shaped schistosomiasis control in Nigeria in the last two decades. We identified some pitfalls in the efforts towards the control of schistosomiasis in the country. We recommended research priority in areas of neglect and advocated for integrated control.

2. Schistosomiasis: correlating interventions with epidemiology

Nigeria is one of the largest countries in Africa in term of population and land mass (Fig. 1). In the last two decades, Nigeria has intensified campaigns against schistosomiasis and other NTDs. The efforts have generated schistosomiasis morbidity reductions in a few endemic areas [8,9]. It is, however, difficult to achieve long term schistosomiasis control implementation programmes. There are strong indications that Egypt, China, Japan, Philippines, and Brazil are progressing towards the elimination of the disease [10]. It appears, however, that the menace of schistosomiasis will last longer in Nigeria. There are no significant differences in the prevalence of schistosomiasis in several states in Nigeria in the different eras (Fig. 2). Nigeria, like many sub-Saharan African countries, depends only on chemotherapy for the control of schistosomiasis. In other countries where considerable efforts towards the elimination of schistosomiasis have been made, chemotherapy is only an integral part of an integrated approach which have helped the countries to achieve a long term control measure [11].

In this review, we described the epidemiology of schistosomiasis in Nigeria using the timeline of some notable landmark global meetings and resolutions involving various actors in schistosomiasis control in the world (Fig. 2). While it was expected to observe a reduction in schistosomiasis morbidity post-2001 WHA Resolution, there was, however, no notable evidence to imply that the WHA's efforts to curtail the transmission of the disease in Nigeria have significantly yielded a positive result. The Southwestern part of Nigeria appears to be most affected with schistosomiasis with the prevalence of infection ranging from 44.8% to 71.5% in endemic areas of Osun and Ogun States (Fig. 2). Although the region is the most versatile in terms of schistosomiasis research in Nigeria, research efforts are yet to culminate in positive development in schistosomiasis control. There is a risk of transmission of

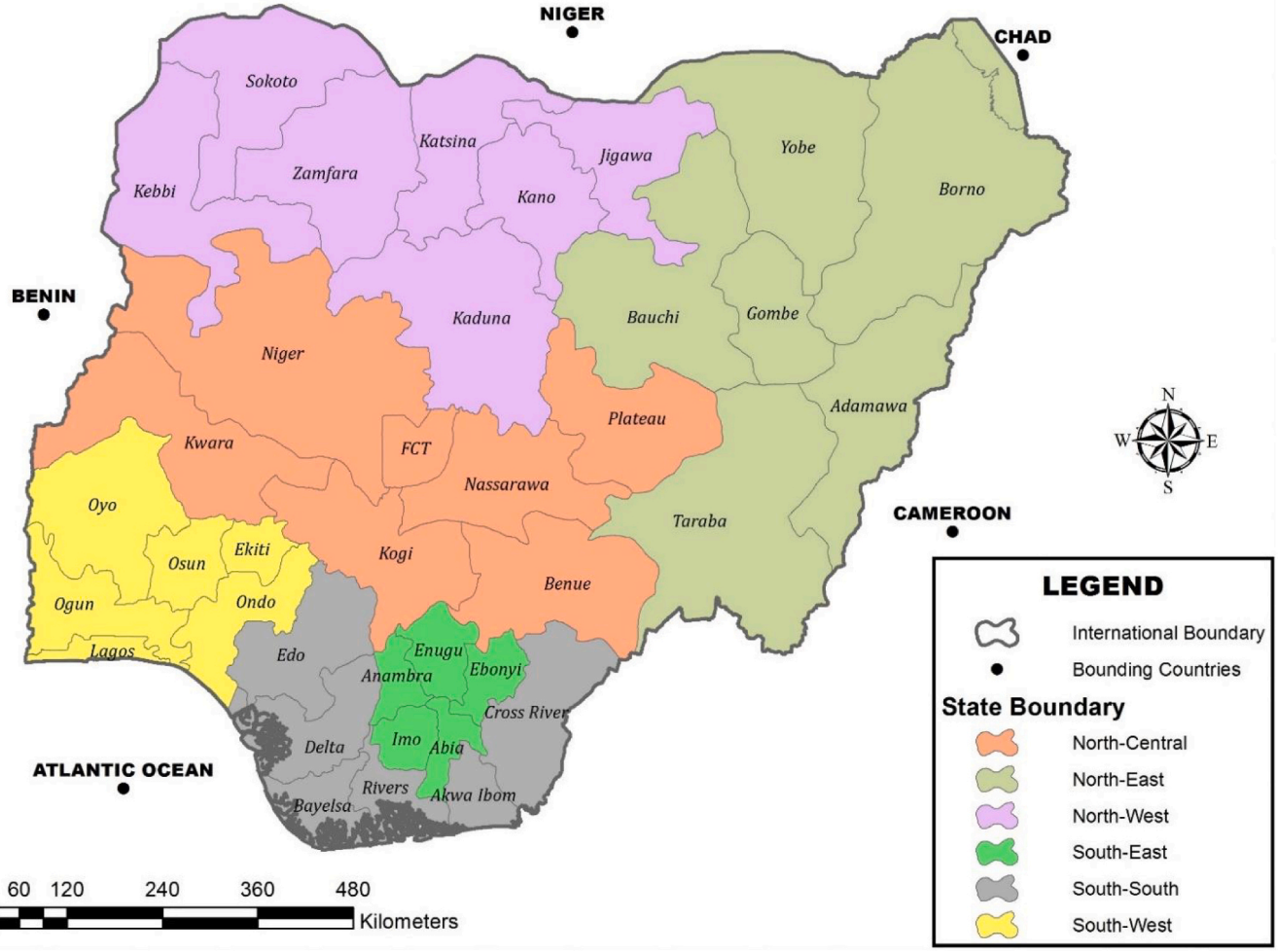

Fig. 1. Map of Nigeria showing the geopolitical zones.
Adapted from https://www.gamers.com.ng/4169-2/

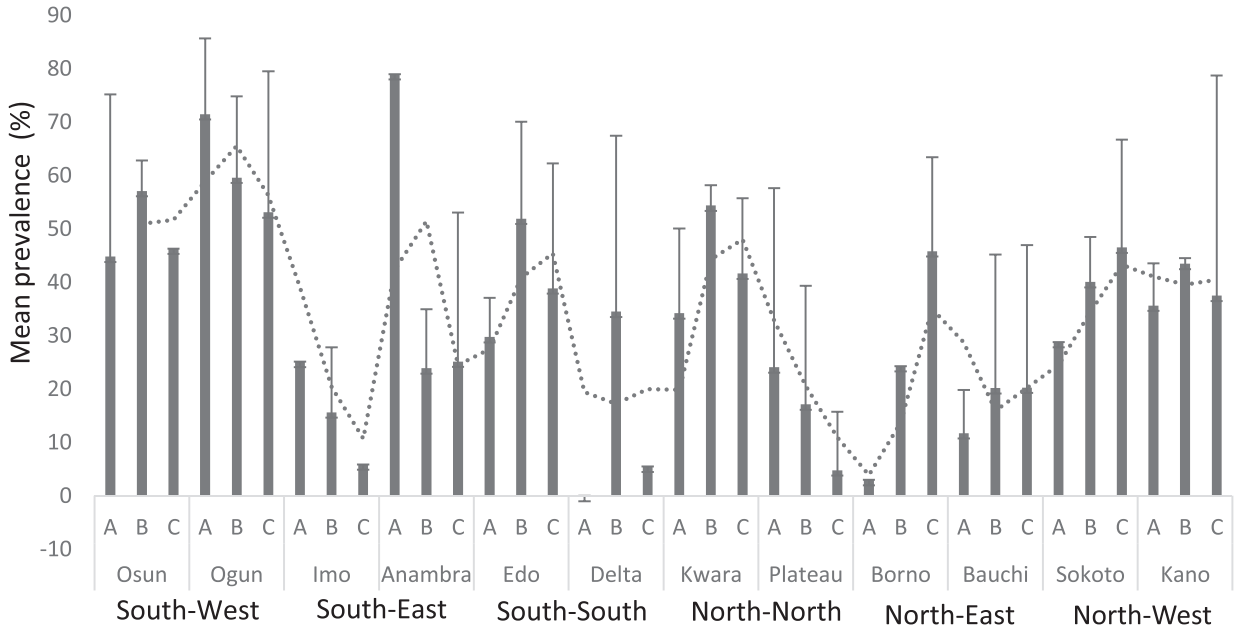

Fig. 2. Epidemiological picture of schistosomiasis in the Nigerian States.
Note: A; on or before the World Health Assembly (WHA) Resolution 54.19 of 2001. B; 2002 to the London Declaration in January 2012. C; Post London Declaration era.

the disease in non-endemic areas as a result of migration [12]. Other than government's intervention to abate transmission in the South-west region, other partners, especially, the non-governmental organisations (NGOs), have their activities concentrated in other regions. The efforts of the Carter Centre Schistosomiasis Control Programme in the South-south (Delta State) and North-central (Plateau State), and other NGOs to complement government's effort in some of these areas could have been responsible for the lower occurrence of schistosomiasis in the regions. However, despite decades of activities of the Carter Centre, schistosomiasis remains a serious public health problem in the areas. The main challenge being sole reliance on chemotherapy-based morbidity control of the disease.

3. Schistosomiasis global health agenda – how is Nigeria faring?

Over the years, several resolutions aimed towards improvement on schistosomiasis control have been made. The World Health Assembly (WHA) in 1975 adopted the call to scale up efforts in drug development, proper engineering design of water management projects, and mobilisation of partners for schistosomiasis control [13]. In 1976, a resolution on the need for endemic countries to put into consideration the epidemiological aspects of the disease during the planning and implementation of water management schemes was passed. In the resolution, the need to implement measures that will help to prevent the spread of schistosomiasis to new geographical locations was also considered [14]. While these efforts recorded some positive outcomes in some countries, the situations in sub-Saharan African countries were rather the same. This 'no result' outcome in sub-Saharan African countries was further complicated in the 1990s by the lack of interest in the schistosomiasis control campaign as other diseases were given more priority in the region's health agenda [15]. It is therefore not surprising that between 1970 and 2001, there was no single record of an epidemiological study on schistosomiasis in some Nigerian States such as Ondo, Nassarawa, Taraba, and Delta States. And obviously, most of the notable schistosomiasis control strategies in Nigeria started in the late 2000s.

In recent years, the control of schistosomiasis and other NTDs has enjoyed greater awareness, as they are now given some level of priority by many governments, international organisations, and donors, and pharmaceutical companies [16]. This recent advancement in schistosomiasis control is a result of other WHA resolutions endorsed in the 2000s. In 2001, the WHO member states endorsed the WHA 54.19 resolution on schistosomiasis and soil-transmitted helminths on attaining at least 75% regular treatment benchmark of all school-aged children in endemic communities by 2010 [5]. While this resolution generated a greater political commitment in many member states, it took Nigeria more than a decade to come up with a national action plan for control of NTDs [17]. This implies that a well-structured schistosomiasis control implementation programme championed by the Nigerian government started in the 2010s. By January 2012, WHO published NTD Roadmap that set targets for the period 2012–2020, and described the strategic approach to accelerate work to overcome the global impact of NTD [18]. During the same period, there was a renewed commitment of partners on the control of NTDs through the endorsement of the London Declaration. The member states and other stakeholders also pledged their support for the WHO Roadmap and its 2020 target. These resolutions received the overwhelming support of pharmaceutical industries who pledged a donation of all required drugs for as long as necessary [6].

In the same 2012, the WHA 65.21 resolution on the elimination of schistosomiasis was endorsed by the WHO member states. The resolution urged all affected countries to strengthen control interventions and surveillance. Importantly, this resolution urged countries to embark on schistosomiasis elimination where possible [18]. In the 2013 WHA 66.12 resolution on NTDs, member states were to take ownership of NTDs' various control programmes [7]. Between 2015 and 2020, three time-bound goals for control of schistosomiasis were set by the WHO NTD Roadmap for the Mediterranean Region, Americas, Western Pacific, and sub-Saharan African countries [16]. Although the WHO NTD Roadmap envisaged the potential elimination of schistosomiasis in some countries in the sub-Saharan region by 2020, it is now certain this feat is unachievable by the end of 2020. Conflict might have contributed in part to the non-realisation of control of schistosomiasis in Nigeria. Although COVID-19 pandemic has been suggested to impede interventional programmes of many diseases, it is not certain that with the level of development in the schisosomiasis control implementation programmes in Nigeria that the WHO NTD 2020 target could have been realized in the absence of the current pandemic.

Nigeria has strengthened the effort to reduce schistosomiasis transmission and morbidity in the recent times. Epidemiological evidence, however, has suggested that the country has a long way to go. A new WHO NTD Roadmap for control or elimination of schistosomiasis is inevitable for Nigeria and many other sub-Saharan African countries.

4. Conflict and schistosomiasis in Nigeria

The impacts of conflict on health have been widely reported [19,20]. Conflict may result in displacement of large proportion of populations into camps with problems of overcrowding and poor shelters, unsafe water and poor sanitation, and increased exposure to disease vectors [21]. The Northeastern region of Nigeria is ridden with religion violence and insurgency. The frequent unrest could lead to under-reporting of schistosomiasis as epidemiological data are often restricted to the relatively safer areas in the region. It is therefore not surprising to have observed a consistent increase in the occurrence of schistosomiasis in the region (Fig. 2). Lack of water supply and destruction of the few available water supply outlets and health facilities might complicate schistosomiasis menace in the region. Many of the most affected rural communities might be excluded from MDA due to inaccessibility resulting from damage of roads during war and non-willingness of health personnel to be deployed to the areas for safety reasons. These underlying problems have led to high prevalence of schistosomiasis among the internally displaced persons (IDPs) who acquired infections from the IDPs' original locations [22], or those exposed to infection as a result of poor socio-cultural conditions and standard of living in the IDPs temporary camps. This calls for IDPs' inclusion in schistosomiasis control interventions as their neglect may stall the success of viable interventions when they are returned to their original communities.

5. Progress in schistosomiasis control in Nigeria

A model has shown that an annual 75% MDA coverage in school-aged children (SAC) and a modest coverage in the adult population would reduce schistosomiasis burden significantly by 2020 [23]. The Nigeria schistosomiasis MDA coverage index is currently at 74% [24], which is a significant increase from 57% recorded in 2016 (Fig. 3). While this appears laudable, this model is not suitable for many endemic areas in Nigeria that require a much higher benchmark coverage index to achieve significant disease burden reduction. The 75% MDA coverage index is more appropriate for areas with low to moderate transmission [23]. The benchmark could have been more suitable for the adult population, however, these individuals are often times excluded from the community's MDA implementation programmes in Nigeria.

Although the Nigerian government in recent times has scaled up efforts on control of schistosomiasis and other NTDs, funds allocation to these diseases are not adequate [25]. Among the NTDs, schistosomiasis is even more neglected, especially in terms of public awareness [26]. Several international organisations and NGOs have come to the rescue over the years.

Since late 1990s, the Carter Centre, through its assisted programme has been playing major roles in schistosomiasis prevention and treatment implementation in six states in Nigeria. The Carter Centre in partnership with the WHO/Merck KGaA (Germany) received a donation of 1.5 million PZQ tablets in 2009 which greatly expanded the Centre's reach in the subsequent years. The generous contributions from other partners have greatly enhanced the Carter Centre's ability to deliver free treatment to more than 1 million children annually in Delta, Ebonyi, Edo, Enugu, Nassarawa and Plateau States in Nigeria [27]. Besides, the Carter Centre, through a partnership with the health authorities of these Nigerian states, has been able to integrate schistosomiasis treatment into other NTDs like onchocerciasis and other helminth infection, thus, reducing the operation cost by about 41% [28]. These efforts appeared to be yielding some results especially in Delta and Plateau States which recorded a reduction in the mean prevalence of schistosomiasis between 2001 and the post-London Declaration 2012 era (Fig. 2). Despite the commendable efforts of the Carter Centre, it is not yet certain that schistosomiasis will be eliminated in these areas soon due to the Nigerian government's non-responsiveness to complement the Centre's effort with provision of potable water to interrupt recurrent transmission in schistosomiasis endemic low-resource communities of these states. In other states like Kano, Jigawa, Yobe, and the Federal Capital Territory, the CBM in partnership with the NGO Health and Development Support (HANDS) has successfully administered schistosomiasis MDA to about 2 million people. Efforts are also made to increase funding

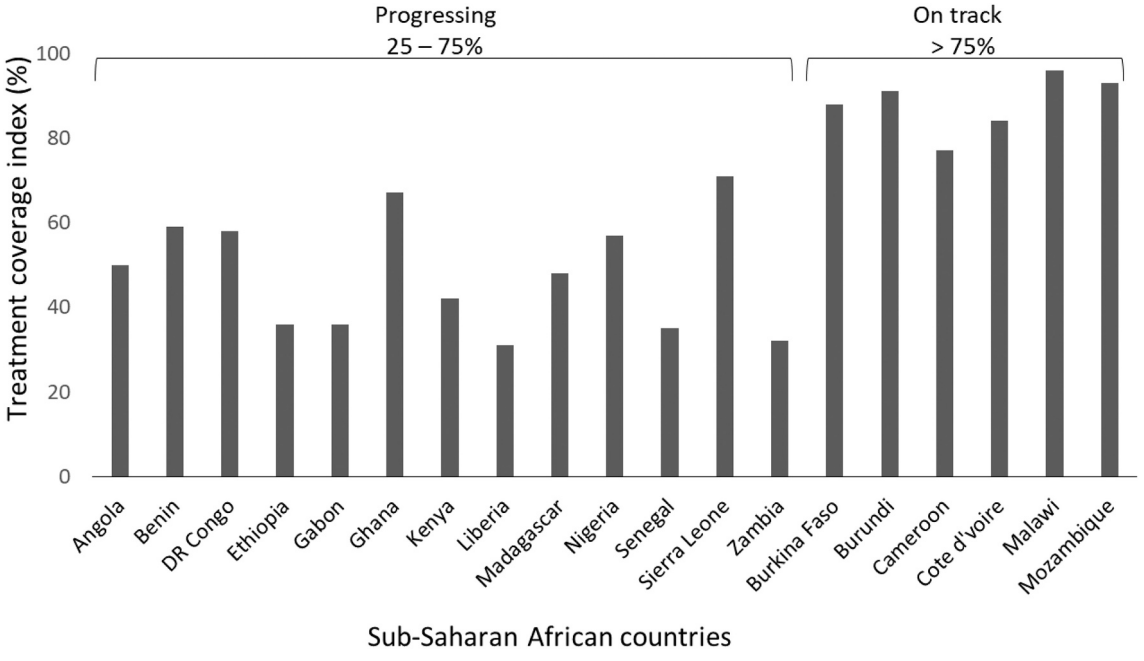

Fig. 3. Praziquantel treatment programme coverage in Nigeria in comparison to other Sub-Saharan African countries.
Note: PZQ coverage index was obtained from https://unitingtocombatntds.org – 2016 data.

to expand treatment coverage for schistosomiasis and soil-transmitted helminths [29].

In early 2020, Merck announced the donation of one billion tablets of PZQ to the WHO of which Nigeria has benefited a delivery of almost 37 million tablets from the same. Merck, through a partnership with the WHO has been fighting against schistosomiasis since 2007 [30]. The END7 funds have supported campaigns against NTDs in Bauchi State [31]. Other NGOs that have partnered with the Nigerian government on schistosomiasis and other NTDs control programmes include Izumi Foundation, Envision, Sight Savers, DFID, and Children's Investment Fund Foundation [32]. Other states not covered by these organisations are meant to be covered under the MDA programmes of the WHO and the Federal Ministry of Health. The implementation of schistosomiasis and other NTDs management policy in Nigeria, however, suffers significantly from bureaucratic bottlenecks in the process of policy development, poor funding from the government, lack of systematic coordination of NTDs programmes at the national and zonal levels, inadequate motivation for personnel and lack of focal data collation officer for NTDs [21].

6. Current challenges in schistosomiasis control in Nigeria

As identified recently, the fight against schistosomiasis might take a longer time than expected if there are no drastic changes in the currently adopted control policy in Nigeria [33]. Despite schistosomiasis being the most studied NTD in Nigeria [34], a report of 21.5% level of awareness about schistosomiasis specific control activities is very low. This is unlike onchocerciasis where public awareness about control programmes seemed to be high [26]. The reason alluded to this encouraging awareness level about onchocerciasis is the fact that onchocerciasis control activities in Nigeria have been ongoing since 1991 [35] unlike that of schistosomiasis that began much more later. Also, the various national and international partners that are leading the onchocerciasis control efforts in Nigeria are visible to the general public [34]. Poor government funding of schistosomiasis control programmes was attributed to the low awareness of control programmes [36]. The implication is that this could lead to wastage of scarce resources deployed to the control of the disease. Inadequate evidence-based public knowledge may also pose a negative impact on policy formulation and implementation.

Experience has shown poorly coordinated schistosomiasis control implementation programmes in some regions of Nigeria. This is usually common in states where there is poor visibility of NTDs control programmes championed by NGOs and international organisations. The poor support from these partners leaves schistosomiasis control programmes largely in the hand of the government who is yet to fully deploy the country's master plan for the control of NTDs, especially schistosomiasis. The limited treatment resources in these regions have led to the adoption of administering treatment only to school children with visible haematuria [33], thus, compromising the recommendation of MDA and leaving a large proportion of infected and high-risk group untreated. In some instances, sub-optimal doses of PZQ were administered to cover a larger population, thus, reducing drug efficacy and posing a possible risk of emergence of PZQ resistant *Schistosoma* strains.

A significant proportion of schistosomiasis infected individuals in endemic areas cannot be accommodated in the community's MDA due to low resources. These individuals who are often attended to in hospitals are left with the option of purchasing PZQ from patent shops. However, a recent study in Nigeria has shown that 50% of PZQ in these patent medicine shops were of low quality [37]. This is even more worrisome as the percentage of poor quality PZQ was found to be higher than other more common drugs in the Nigerian market in Kano metropolis (Fig. 4). The poor quality of PZQ was reported not to be associated with the prices of the different brands [37] and could result in an apparent low cure rate of the standard dose of the drug [38].

7. Improving interaction between research and Ministry of Health

The bane of schistosomiasis burdens and other NTDs cannot be separated from the neglect of some research priority areas which could have aided control efforts. Epidemiological studies abound on schistosomiasis, and it is in fact, the most studied NTD in Nigeria [34]. The advantage schistosomiasis has over other NTDs could be due to the ease of diagnosis of the disease. On many occasions, *S. haematobium* is used as an indicator of endemicity of schistosomiasis in an area because of its relatively easier diagnostic procedures involving the use of urine for both microscopy and indirect diagnosis using simple chemical reagent strips [39]. It is, however, observed that epidemiological studies are skewed towards gathering, most of the time, only prevalence data. On many occasions, these studies were not purposefully conducted for interventional programmes as there exists a limited synergy between researchers and the Ministry of Health [39].

The Nigeria Centre for Disease Control (NCDC), an arm of the Nigerian Ministry of Health, emphasises one health approach towards disease control through evidence-based prevention, integrated disease surveillance and response activities. Most of the schistosomiasis control responses in Nigeria are however not evidence-based and integrated

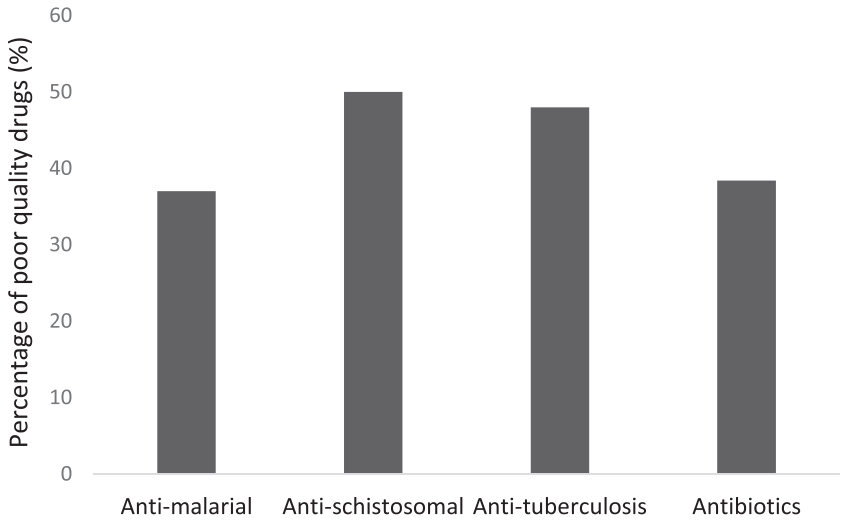

Fig. 4. Quality assessment of praziquantel relative to other anti-infectious agents' drugs.

control measures have not been adequately stressed. Government bureaucracy in national health matters often times limits the extent to which researchers can contribute in decision making in health-related matters including that of schistosomiasis. This distorted relationship has negative impact on schistosomiasis control which is not adequately prioritised in the national health agenda.

8. Schistosomiasis mapping efforts in Nigeria

The mapping of disease distribution plays a crucial role in their control. The mapping of NTDs including schistosomiasis is necessitated by weak disease surveillance resulting in incomplete and unreliable national reporting [40]. It is an important tool for identification of communities that would require preventive treatment with PZQ. Early studies on mapping of schistosomiasis involved the generation of predictive schistosomiasis transmission risk maps in Ogun State [41]. In 2013, a nationwide mapping and prediction of schistosomiasis in Nigeria was undertaken [42]. Others have been conducted in different states of the country [43,44]. Few studies have also identified schistosomiasis transmission foci by mapping out areas with abundance of freshwater snails that serve of intermediate hosts of schistosomes [45,46]. While these are necessary for abating transmission of schistosomiasis in Nigeria, it is not certain if the outcomes of such efforts were ever adopted in planning schistosomiasis control implementation programmes in the Nigeria: many high-risk zones identified in mapping are yet to be captured in MDA.

9. Snail intermediate hosts as important component of integrated control

Countries where control of schistosomiasis have been significantly achieved have prioritised snail control as much as MDA. In China, advocacy on snail eradication is so strong and is still regarded as the most effective way to eradicate schistosomiasis [47]. In Nigeria, very few studies are available on freshwater snail-schistosome relationship. While it is generally believed that *Bulinus globosus* and *Biomphalaria pfeifferi* are the main intermediate hosts of schistosomes in Nigeria, new evidence has suggested other possible hosts like *Bulinus jousseaumei* and *B. camerunensis* for *S. haematobium* [48–50]. Many malacological studies related to schistosomiasis are hampered by the lack of modern tools to carry out proper identification of snails and detection of infection in snails found in freshwater bodies in schistosomiasis endemic areas. At the moment, nothing is known about gene expression in snails and their roles on susceptibility to *Schistosoma* infection, and the impact of aquatic pollution on the transmission of schistosomiasis in Nigeria. There are also no studies on hybridization in *Schistosoma* spp. and implication on snail-parasite interactions. Hybridization could lead to acquisition of new genes which can result in generation of new strains of parasites with differed virulence and pathology. This could necessitate new control starategies in areas where this is common. These are areas of neglect that need urgent attention for the implementation of integrated schistosomiasis control policy in the country.

10. Prioritising schistosomiasis research in neglected groups and areas

Epidemiological studies have been grossly skewed towards school-aged children for decades in Nigeria and other African countries. While it is undeniably true that the school children are the most at-risk group, epidemiological evidence has recommended the inclusion of other population substrata in schistosomiasis control implementation programmes. Advocacy has been strongly made for the inclusion of preschoolers and pregnant women or women of reproductive age in schistosomiasis MDA. Since the last two decades, research interest in schistosomiasis among preschoolers is gradually gaining ground in Nigeria [51–53]. However, a good percentage of this population is not included in MDA since most MDAs in Nigeria are school-based. This neglect could spell grave consequences on the preschoolers' population due to morbidity build up over a while especially in a country where yearly MDA cannot be guaranteed. The case of pregnant women could be worse as they have been consistently excluded from MDA despite the risk *Schistosoma* infections could pose to both the mother and the unborn child. Studies on maternal schistosomiasis are still scanty in Nigeria [1,39,49], and the Ministry of Health is yet to adopt the WHO recommendation of their inclusion in treatment [54]. There is a need for priority to be given to schistosomiasis research in pregnant women owing to the disease associated-sequelae which can result in poor pregnancy outcomes like low birth weight, abortion, still-birth, and maternal death [55].

Because it takes a long time for schistosomiasis chronic disease to manifest, its public health importance has been seriously downplayed. However, besides the great burden schistosomiasis could pose on the affected population, it is one of the NTDs that is closely associated with several other diseases like HIV/AIDS, malaria, bladder cancer, poliomyelitis, hepatitis, and urinary tract infections [56–62]. When *S. haematobium* finds its way into the female genitalia, it can cause primary and secondary infertility, and other disease sequelae which promote other infections like HIV and human papilloma virus (HPV). The latter has been implicated in cervical cancer and genital *S. haematobium* infection has been hypothesised to be an additional co-factor or even an independent risk factor for cervical neoplasia [63]. Unfortunately, the association between female genital schistosomiasis (FGS) and HPV is yet to be explored in Nigeria despite the increasing cases of cervical cancer in the country. As a matter of fact, despite the occurrence of *S. haematobium* infection in women of reproductive age in Nigeria [39,49], little is known about FGS and associated risks in women in Nigeria. This is in constrast with experience in some African countries where a number of resources around FGS including a 'colposcopic atlas' are available [64,65].

While schistosomiasis transmission is more skewed to the rural and peri-urban areas in Nigeria, there is still some evidence of focal transmission of the disease in urban areas [66]. In Nigeria, many rehabilitation homes are situated in cities. These homes sometimes harbour children from areas of the country that are endemic for schistosomiasis [67]. Therefore, these areas with focal distribution of the disease should be given consideration in the national schistosomiasis control implementation programmes regardless of the location.

11. Conclusions

Much more is still needed to be done if the battle against schistosomiasis is to be won in Nigeria. Although the PZQ treatment coverage index has significantly increased in the last five years, the transmission is still unabated. The implication is that schistosomiasis control cannot be sustained only by MDA. Other components of integrated control, should be adequately reviewed and implemented to achieve the desired results. Water sanitation through prevention of defaecation or urination in water bodies, provision of potable water, education, and snail control should be prioritised. The practice of implementation of MDA only in school children should be reviewed due to the grave consequences that non-treatment can pose to other vulnerable populations like preschoolers and pregnant women. More research is solicited for a better understanding of the transmission dynamics and impact of comorbidity with other infectious agents on humans. More importantly, more is needed on the biology of potential snail hosts of schistosomes and the identification of molecular markers that can aid transmission. Studies on FGS and its impact on reproductive health, the association of FGS with HPV, and other infectious agents are as well recommended. The prioritisation of schistosomiasis and other NTDs programmes is long overdue and this should include high-level advocacy to policymakers for release of counterpart funds and increased funding of these diseases. There is a need to complete the mapping of schistosomiasis where no

mapping has been done and a deliberate adoption of the mapping for planning schistosomiasis MDA implementation programmes is highly recommended. System strengthening to ensure efficient delivery of zonal and national officers on schistosomiasis and other NTDs control implementation programmes should be prioritised.

Ethical statement

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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