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Control of Schistosomiasis

Monday Francis Useh
University of Calabar, Calabar
Nigeria

1. Introduction

Schistomiasis is a disease caused by digenetic trematodes that belong to the family Schistosomatoidae. Five species of Schistosomes are involved in human infection. The three principal agents are *Schistosoma mansoni* and *S. japonicum* which are responsible for intestinal schistosomiasis and *S. haematobium*, the aetiologic agent of urinary schistosomiasis. The other two species responsible for intestinal disease though with low frequency are *S. intercalatum* and *S. mekongi*. The disease affects about 240 million people worldwide while an estimated 779 million people (more than 10% of the world population) are at the risk of infection. About 120 million people infected with schistosomiasis are estimated to be symptomatic while about 20 million develop severe diease.The disability-adjusted life years (DALYs) due to schistosomiasis is about 1.7-4.5 million while between 150,000 to 280,000 people are known to die as a consequence of the disease per year. Africa accounts for 85% of the disease burden (Steinmann *et al*., 2006; WHO, 2002). Although, schistosomiasis is a rural focal disease typically associated with poor rice farmers and fishermen in the tropics, it is increasingly been reported among Europeans with a history of travel to endemic areas in Africa and Asia. It is transmitted by snails found in cercariae infested fresh water streams. Snails belonging to the species *Bulinus, Biomphalaria* and *Onchomelania* are the vectors of *S. haematobium*, *S. mansoni* and *S. japonicum* respectively.

The cardinal objective in the control of schistosomiasis is the reduction of morbidity and mortality to levels below public health significance. Over the years, emphasis has shifted from the non-realizable goal of eradication to the more realistic goal of morbidity control. In this context, Gemmel *et al* (1986), defined "a control programme" as the "implementation of specific measures by a disease control authority to limit the incidence of the disease". Such implementation may involve specific technical interventions and perhaps legislation to enforce compliance. The success of this type of approach is predicated on an accurate ecological diagnosis, that is, a diagnosis of the human community, its parasitological characteristics, its physico-geographical environmental attributes and man's behavioural attitudes and customs (Davis, 1981).

The enormous morbidity associated with schistosomiasis which ranks it next to malaria in terms of public health significance re-emphasises the need for a coordinated and sustainable means for the control of the disease. There is a consensus of opinion that the control of the disease should be integrated. In this model of control, King (2009) identified the applicable approaches as:

- Population based chemotherapy
- Snail control which involves habitat modification and use of plant and chemical molluscicides,

- Proper treatment of sewage,
- Good environmental engineering designs for the development of irrigation and hydroelectric schemes to limit the availability of breeding grounds for the snail vectors
- Provision of clean and safe piped water and
- Massive health education and mobilization of the population to claim ownership of the programme

In this Chapter, the various methods of control of schistosomiasis listed above are reviewed with special emphasis on those that are accessible, affordable, acceptable and capable of yielding high levels of sensitivity and specificity. Chemotherapy which is the most feasible method of morbidity control of the disease particularly in the short-term is examined in more details. In the process, the hindrances to an effective integrated control approach are identified while recommendations on the way forward are proffered. There is no doubt that vaccination holds the key for the cost effective and sustainable control of infectious diseases including schistosomiasis. The progress made in the identification of probable candidate antigen molecules for the control of schistosomiasis is also examined. The basis of this composite approach is to gradually reduce the morbidity due to schistosomiasis. This is likely to result in the drastic reduction in the number of infected subjects and environmental egg pollution. Where this is sustained, infection would no longer be of public health significance.

2. Control of schistosomiasis

The first control programme for schistosomiasis was initiated in 1913 in Egypt where both local people and stationed soldiers were heavily infected. This was anchored on snail control. The effectiveness of the programme was based on the numbers of snails killed and not reductions in the numbers of infections (Jordan, 2000). Mass treatment with tartar emetic was also an integral part of the process although the results were not encouraging. About the 1930s, sanitation was incorporated in the programme, but still the results were not convincing (Jordan & Rosenfield, 1983). Following the elucidation of the life cycle of Schistosomes by Lieper during the first years of the first world war, snail control and mass treatment became the model of control efforts. Jordan (2000) noted that together with recommendations on a number of environmental control measures, Leiper considered it possible to eradicate the disease without the cooperation of the infected individuals by destroying the snail intermediate host. Blas *et al* (1989) reports that the first control programme that integrated research and systematic monitoring of its effect was implemented in Lyte in the Philippines from 1953 to 1962 with the help of the WHO. The initial objective of the schistosomiasis control was aimed at stopping transmission. This could hardly be achieved and remains elusive even up till today.

The WHO Expert Committee on Epidemiology and Control of Schistosomiasis took a holistic approach at the control of the disease and noted that "comprehensive understanding of the environment, demographic, social, human behavioural and economic factors" in schistosomiasis is essential for the design of control programmes that are successful in the long run (Kloos, 1985). With the advent of praziquantel (PZQ) as a safe and efficacious drug for the treatment of schistosomiasis, the WHO in 1991 reinforced its 1984 recommendation to shift from transmission control (focusing on the prevalence of infection) to morbidity control (laying emphasis on intensity of infection) (Bruun and Aagaard-Hansen, 2008). Morbidity control will not only reduced the number of people infected but it will also drastically reduce environmental contamination with the eggs even when cure is not attained. A drastic

reduction of the pollution of the environment with the eggs would also reduce the chances of transmission. Should this occur at a level below public health importance, the probability of eventually elimination of disease is certain with a sustained integrated approach

3. Chemotherapeutic control of schistosomiasis

Of all the methods of control listed above, chemotherapy is the only one that is widely used presently in endemic areas for the control of morbidity due to schistosomiasis. Among the first group of drugs used for the treatment of schistosomiasis included; Antimonials, Niridazole, Hycanthone, Lucanthone, Oxamniquine and albendazole. PZQ is currently used for the treatment of all the species while metrifonate is active against *S. haematobium* only. Recently, artemisinins earlier synthesized for the treatment of malaria infection is being used in some endemic communities to treat schistosomiasis. The WHO (1993) identified four approaches in the administration of chemotherapy programme namely;

i. Mass treatment: treatment of the entire population. This is often limited by availability of finance.
ii. Selective population treatment: treatment of infected persons identified by a diagnostic survey of the whole population
iii. Selective group treatment: treatment of all or infected members of a high risk age or occupational group
iv. Phased treatment: use of the above strategies in a sequence of progressively greater selectivity.

It is recommended that treatment should be administered to schoolchildren who are the most vulnerable group through the school system. The outcome of basing treatment on the school system is bound to give variable results. In an area endemic for urinary schistosomiasis in Nigeria, Useh and Ejezie (1999a) showed that relying on the school system alone to deliver control programme may substantially limit the outcome of control of schistosomiasis. The rates of regular, irregular and non school attendance were 69.1%, 5.1% and 25.8% respectively. Out of school children were more associated (90.7%) with *S. haematobium* infection than those in school (86.8%). The authors recommended a dual method of control that would incorporate the integration of recognized local authorities in areas with moderate school attendance like their study area as lack of treatment of infected out of school children would ensure continuous contamination and re-infection. (See Table 1)

Gender	Regular School Pupils, No(%)	Irregular School Pupils, No(%)	Children Out of School, No(%)	Total
Male	889(76.6)	50(4.3)	222(19.1)	1161
Female	699(61.4)	67(5.9)	372(32.7)	1138
X^2	58.02	2.77	55.86	NA
Odds Ratio	2.020	0.72	0.48	NA
95% CI	1.69-2.42	0.49-1.04	0.4-0.58	NA
P	<0.0001	>0.05	<0.0001	NA

(Adopted from Useh & Ejezie, 1999a)

Table 1. Frequency of school attendance and non-attendance by sex of school-age children in Adim, Nigeria.

This recommendation is supported by a study conducted in Tanzania on the effect of community-directed treatment approach (ComDT) versus the school-based treatment approach on the prevalence and intensity of schistosomiasis and soil-transmitted helminthiasis (STH) among schoolchildren (Massa *et al.*,2009). The prevalence of *S. haematobium* and Hookworm infections were significantly lower in the ComDT approach villages compared to the school-based approach villages (10.6 versus 16.3%, P = 0.005 and 2.9 versus 5.8%, P = 0.01, respectively).

3.1 PZQ

3.1.1 Biochemical properties and pharmacokinetics

PZQ is the drug of choice for the treatment of schistosomiasis. It is a broad spectrum anti-schistosomal which is principally active against the adult stage of all the schistosome species infective to man. It is a 2-cyclohexycarbonyl 1,2,3,6,7,11b-hexahydro-4H-pyrazino(2,1-a Isoquinolin-4one) compound with a melting point at 136-140C. It was developed in the laboratories for Parasitological Research of Bayer AG and Merck KGaA in Germany (Elbert and Darmstadt) in the mid 1970s. It has a molecular mass of 312.411 with a serum half life of 0.8 to 1.5 hours in adults with normal liver and kidney function and is mainly excreted in urine. PZQ is a white crystalline powder with bitter taste. It is stable under normal storage conditions. Although, it is insoluble in water, it is soluble in chloroform, dimethylsulfoxide and ethanol. It is sold as a racemate mixture consisting of equal parts of 'laevo' and 'dextro' isomers, of which only the laevo component displays anti-schistosomal properties.

The recommended dose of PZO is 40 mg/kg body weight. The drug is available as a 600mg tablet. The quality of PZQ (proprietary and generic) currently available in the market is quite high. Thirty four PZQ samples from different manufacturers were collected at the user level in various countries and subjected to quantitative analysis of active ingredient, purity, disintegration and dissolution in accordance with established pharmacopoeial standards. The results showed that most of the samples were of high quality except two samples from the same manufacturer that had no PZQ (Sulaiman *et al.*, 2001). About 90% of the damage done to organ function are known to reverse six months following the administration of PZQ. Although it is exceptionally well tolerated, reported side –effects include abdominal discomfort, nausea, headache, dizziness, drowsiness and pyrexia especially in subjects with high egg counts (Andrews,1981).

3.1.2 Mode of action of PZO

The mode of action of PZQ has been extensively reviewed elsewhere (Doenhoff *et al.,* 2008 & 20009). The exact mechanisms of action of PZQ is still poorly understood. PZQ is known to induce rapid calcium influx that distort the morhoplogy and physiology of schistosome. Jeziorski and Greenberg (2006) showed that the B subunits of voltage-gated Ca^{2+} channels is the prime molecular target of PZQ. It has recently been reported that cytochalasin D abolished the schistosomicicidal activity of PZQ but calcium influx into PZQ exposed schistosomes was not halted. This result therefore raises doubts whether calcium influx is essential in the antischistosomal activity of PZQ (Pica-Mattoccia *et al.*,2008). PZQ induces contraction of schistosomes which manifest in paralysis in the contracted state. Additionally, vacuolation and blebbing near and on the surface of the worm have equally been reported (Pax *et a*l., 1978).

PZQ is known to increase exposure of antigens on the worm surface. It is believed that this in turn renders the worm more susceptible to antibody attack. Doenhoff *et al* (1987)

inferred that this drug induced antigen exposure is assumed to account for the synergistic effect between PZQ and the host antibodies in killing worms invivo. Recently, it has been shown that PZQ seems to interfere with adenosine uptake in cultured worms. This may have therapeutical relevance given that the schistosome is unable to synthesize purines such as adenosine *de novo.* It may be assumed that the drug interferes with schistosome's obligate need to acquire adenosine from its host. This is confounding as a relationship between Ca^{2+} channels and adenosine receptors has been demonstrated in cells of some other animals and adenosine can antagonize Ca^{2+} release. This informs the inference drawn by Angelucci *et al* (2007) that PZQ-induced Ca^{2+} influx and adenosine receptor blockade may be connected.

3.1.3 Field studies on the efficacy and effectiveness of PZQ

It is important to understand the difference between efficacy and effectiveness as applicable to anthelminthic drugs in field trials. The WHO (2002) defined efficacy as the "effect of a drug against an infectious agent, in isolation and under ideal conditions" while effectiveness refers to the "effect of the drug against an infective agent under operational conditions". Following from the above, effectiveness may be influenced by factors such as patient compliance with treatment, and by ecological, immunological, or epidemiological factors confounding by ongoing disease transmission. Thus the main markers of effectiveness of large-scale deworming exercise is the general improvement in health status of the population at risk and also taking into consideration other important variables such as cost of drug delivery, accessibility and acceptability of treatment, and sustainability. Efficacy and effectiveness are measured using qualitative and quantitative tests for eggs in faeces or urine. Cure rates and egg reduction rates are used to measure the response to treatment. These indicators are simple and easy to determine under field conditions. It is important to note that the qualityof results derived are dependent on the parasitological techniques used and on the time after treatment at which prevalence and intensity of infection are evaluated.

PZQ has been associated with a cure rate of between 60-90% and sometimes egg reduction rate of up to 95% in different community- based studies. A complete cure of all study participants (100%) has not been achieved. In an endemic community in Nigeria, this author and colleagues have shown that the pre-treatment prevalence of *S. haematobium* of 71% with microhaematuria and proteinuria of 83% and 94% respectively declined to 23%, 27.5% and 19% respectively after two annual treatments with PZQ. As a result of the high cost of the drug and the labour intensive diagnostic methods involved, the authors recommended that chemotherapy should be given at yearly intervals to targeted school-age children (Ejezie *et al.,* 1998). The implication of this recommendation is that the money invested in diagnosis could be used in the procurement of more tablets of PZQ. In this same group of schoolchildren, the educational pass rate improved following the first treatment session from 81.4% to 90.7% but later declined to 84.2% following the second treatment session. The net improvement in school performance was statistically significant (X^2 = 7.2; P= 0.027) (Meremikwu *et al.,* 2000).To buttress their findings, the authors noted that the possibility of enhancement of educational performance as observed in the study should make regular, periodic treatment of children in communities with endemic schistosomiasis a more cost-effective and beneficial public health intervention strategy than was previously assumed. kabatereiene *et al* (2003) reported a cure rate of 69% and egg reduction of 97-99% in individuals treated for *S. haematobium* infection in

Uganda. In a related study in Cameroon, a higher cure rate of 83-88.6% and egg reduction rate of 98% was reported following the administration of a standard dose of PZQ (Tchuente *et al* ., 2003).

There are reports of disappointing cure rates with PZQ. In an area of intense *S mansoni* transmission in northern Senegal, PZQ administered at the standard dose gave a cure rate of 18-36% (Gryseels *et al.,* 1994). Subsequently, the dose was increased without any significant improvement in the efficacy rate (Guisse *et al*., 1997). However, when treated with oxamniquine, there was a significantly higher cure rate (Stelma *et al*., 1997). Relatedly, Ismail *et a*l (1999) treated 1607 *S. mansoni*-infected patients in Egypt with PZQ at 40 mg /kg and, after an additional two treatments, the last at 60mg/kg, 1.6% of the patients were still passing viable eggs. It is remarkable that these low cure rates are more associated with *S. mansoni* than *S. haematobium* infection.

In 2001, the World Health Assembly set a target of treating about 75% of schoolchildren infected with schistosomisis and soil-transmitted helminthes. This target is yet to be met. Available data showed that 18,151, 619 and 19,570,971 infected subjects were treated with PZQ in 2008 and 2009. Of this, 14, 498,101 subjects in Africa were treated. This statistics is based only on countries rendering treatment reports to WHO. Were all endemic countries to report, it is likely to be higher as more infected people now have access to PZQ and could afford treatment. Unlike in the 1980s and 1990s, PZQ is now cheap and affordable. The average price is about US$ 0.10/tablet or less (WHO, 2003).

The availability of a dose pole which is based on height for the administration of PZQ is another innovation for the ease of community-based studies unlike the previous situation of measuring the weight of pupils. Weight measurement was limited by the sensitivity of the balance used which in some instances could lead to under or over dosing. Montresor et al (2001) reported on the validation of dose pole using existing data. This validation confirmed 98.6% of school-age children would have received a PZQ dosage between 30 and 60 mg/kg body weight, and that 84.7% would have been between 40 and 60 mg/kg. Corresponding figures for the whole populations (including young children and adults) were 95.5% and 68.2%. The validity of an extended PZQ dosing pole has been tested in Uganda (Sousa-Figuriredo et al., 2010). The extended dose pole was found to be very accurate within Uganda as well as in Zanzibar (prevalence levels of acceptable dosages estimated were 98.6% and 97.6%, respectively). It is thus considered to be a reliable and practical method for determining the dose of PZQ needed to treat schistosomiasis.

3.1.4 Resistance of Schistosomes to PZQ

Drug resistance is defined as "a genetically transmitted loss of susceptibility to a drug in a parasite population that was previously sensitive to the appropriate therapeutic dose" (WHO,1996). Currently, molecular biologic techniques are not available for the detection of resistance of schistosomes to PZQ. The resistance of Schistosomes to PZQ has recently been examined (Botros and Bennett, 2007). It cannot be scientifically ascertained whether cases not cured as encountered in the Senegalese and Egyptian studies were cases of resistance or drug tolerance. It has been noted that PZQ is partially immune dependent. Lack of acquired immunity in Northern Senegal where Schistosome infection was newly introduced may have perhaps accounted for the low cure rate. Remarkably, Fallon and Doenhoff (1994) were the first to point to a possible development of resistance as mice infected with *S. mansoni* were insensitive to PZQ.

In a related study, Fallon *et al* (1997) reported that a parasite line derived from an isolate from Senegal was less susceptible to PZQ than other isolates used as controls. Another supportive evidence can be deduced from the work of Ismail *et al* (1996). Several isolates were established in laboratory- maintained life cycles from eggs passed by uncured patients, and adult worms of these isolates were found to have PZQ ED 2- TO 5- fold higher after PZQ treatment in mice than isolates that had been established from eggs before treatment by patients who had been cured.

PZQ is known to kill the adult worms and not the immature stages. It is possible that the uncured subjects were harbouring the immature stages of the parasite at the point of treatment. As a follow up to this, a protocol was suggested for screening for suspected instances of PZQ resistance; this consisted of administering two doses of the drug, 2-3 weeks apart, so that the second would eliminate any schistosomes that had matured in the interval (Renganathan and Cioli, 2000). The utilization of this protocol in Northern Senegal achieved the expected higher cure rates (Picquet *et a*l.,1998).

The issue of schistosome susceptibility or resistance to PZQ is further confounded by the fact that PZQ failed to cure a schistosome infection that was acquired by travelers or military personnel in endemic countries after returning to their non-endemic country of origin (Silva *et al*., 2005).

It is difficult to dismiss the high rate of uncured subjects in Senegal which were subsequently cured upon the administration of Oxamniquine as not being due to resistance. However, in the absence of a clear scientific tool to detect resistance, there is need for vigorous monitoring of the efficacy of PZQ as it remains a drug of choice for the treatment of schistosome infection in the foreseeable future. Additionally, there is a consensus of opinion that drug manufacturers and researchers should commence a sustained search for an alternative drug to PZQ. Ro 15-5458 is one of such candidate compound discovered about 20 years ago by Hoffman-La Roche (Basel, Switzerland). Administered, at a single dose, it was highly efficacious against both the immature and adult worms (Sulaiman *et al.,* 1989; Pereira *et al.,* 1995). Another prospective candidate compound is 2-(alkylamino)-1-phenyl-1-ethanethiosulfuric acid. It has been attributed with the elimination of a very high population of female schistosomes than male worms in a mouse model. A lot of studies are required before it can be used for the treatment of infected human subjects (Moreira *et al*., 2007).

3.2 Oxamniquine

3.2.1 Molecular structure and pharmacokinetics

Oxamniquine was first described in the late 1960s. The compound is 6-hydromethyl-2-isopropyl-aminomethyl-7-nitro 1,2,4-tetrahydroquinoline. It is produced by biological processes. The drug is administered as 15mg/kg body weight for adults while children are treated with 20mg/kg given in two doses of 10mg/kg each in an interval of 3-8 hours. It is extensively metabolised through oxidation process. The metabolites are active and excreted in urine. The side effects are mild, transient and well tolerated especially when given after a meal (Utizinger *et al*., 2003).

3.2.2 Mode of action

Unlike PZQ, the mechanism of action of oxamniquine is fairly well understood. Oxamniquine is only active against *S. mansoni* but not effective against *S. haematobium* and *S.*

japonicum. The active ingredient is tetrahydroquinoline which acts on the adult *S. mansoni* and immature invasive stages, with males more susceptible than the females. Its anticholinergic effect, which increases parasite motility and inhibits nucleic acid synthesis, has no notable effect on the other *Schistosome* species (Secor & Colley, 2005). The mechanism of action of oxamniquine is related to irreversible inhibition of nucleic acid metabolism of the parasite. The drug is activated in a single step, in which the *Schistosoma* enzyme converts the oxamniquine to an ester, and spontaneously dissociates resulting in an electrophilic reactant and alkylation of the Schistosoma DNA. Worm death is associated with the formation of sub-tegumental vesicules in adult parasites. Different responses are observed after therapy, with less specific morphological alteration and hepatic shifts, occurring over a period of six days post treatment (Utzinger *et al*., 2003).

3.2.3 Application of oxamniquine in *S. mansoni* control programmes

Oxamniquine is not used widely for the control of *S. mansoni* infection particularly in Africa because it is more expensive than PZQ. The fact that it proved more effective than PZQ in an endemic focus in Northern Senegal where PZQ gave an embarrassing low cure rate still recommends its usage. However, the drug is widely used in Brazil and other South American Countries for the control of *S. mansoni* infection. Katz and Coelho (2008) reported that over 12 million doses of the drug were administered in a control programme in Brazil alone.

3.3 Metrifonate

Metrifonate was initially introduced as an insecticide in 1952, but later in 1960, it was used to treat helminth infection. The drug also refer to as trichlorophone is a cheap organophosphorus ester which is only active against *S.haematobium*. It is rapidly absorbed, metabolized and excreted. The metabolic pathway yields DDVP (2,2-dichlorovinyl dimethylphosphate), a cholin esterase inhibitor which is the active compound. The mechanism of action is not known. It is relatively cheap and is not toxic. Metrifonate is administered as 7.5-10 mg/kg body weight, given in three divided doses in two weeks interval. Among the side effects reported following the administration of the drug include abdominal pains, diarrhoea, fatigue and muscular weakness which dissipates within 12 -24 hours (Danso-Appiah *et al.,* 2008). The reasoning behind the widely spread dosage has to do with its inhibitory effects on red cells and plasma cholinesterase.

Metrifonate is not used currently for the treatment of urinary schistosomiasis. Several reasons account for this. One of which is poor compliance by patients as a result of the spacing and multiple dosing. The second reason is reduced level of efficacy. For instance, Mgeni *et a*l (1990) reported a cure rate of 40% and egg reduction rate of 90% in Zanzibar. Lastly the advent of PZQ with its superior efficacy rate and broad spectrum activity meant that it was no longer cost effective and sustainable to rely on metrifonate.

3.4 Artemisinin and its derivatives

3.4.1 Biochemical characteristics and pharmacokinetics

The artemisinins though syntheised for the treatment of malaria is the newest drug used for the treatment of schistosomiasis. Unlike PZQ, which is active against the adult stages of the parasite, artemisinin is active against the immature stage of parasite. It is a sequitterpene lactone with a peroxide group, obtained from the leaves of the plant,

Artemisia annua which are grown in Central Europe, China, USA and Argentina among others. The major derivatives of artemisinin are artesunate, artemether, arteether with dihydroartemisinin as the principal active metabolite. Primarily they are antimalarials, but the anti-schistosomal properties were discovered by Chinese scientists in the 1980s especially for the treatment of *S japonicum* infection (Hommel, 2008). They are well tolerated with only minor side effects.

3.4.2 Mode of action of Artemisinin

The precise mode of action of this drug is not known. Artemether is the most potent. It exhibits the highest level of activity on one to three weeks old liver stages of the parasite. When a dosage of 6mg/kg weight is administered, it kills the schistosomulas during the first 21 days. The invasive and adult stages are less affected and the adult females are more susceptible than the males (Allen *et al*., 2002). Following treatment, artemether induces severe and extensive tegumental damage and significant reduction in glycogen contents through the inhibition of glycolsis, but the onset of this alteration is slow. It also hinders the development of egg laying adult worm pairs (Xiao et al., 2000).

3.4.3 Efficacy of artemisinin in field studies

Several studies have been carried out to test the feasibility of using artemisinin for the treatment of schistosome infection. The efficacy of oral artemether for prevention of *S mansoni* infection was investigated in Western Cote d'Ivore (Utzinger *et al*., 2000). The group that received artemether had a significantly lower incidence of *S mansoni* infection (31/128 versus 68/140, relative risk: 0.50 [95% CI 0.35-0.71], P=0.00006). The geometric mean egg output among positive children in the artemether group was significantly lower than in the placebo group (19 vs 32 eggs/g stool, p=0.017). The authors recommended the use of artemether in an appropriate situation as an additional tool for the control of intestinal schistosomiasis. In the same country, the activity of artemether against *S haematobium* infection has also been assessed. The incidence of patent *S. haematobium* infections in artemether recipients was significantly lower than in the placebo recipients (49% vs 65%, protective efficacy: 0.25, 95% CI: 0.08-0.38, P=0.007). The geometric mean intensity in the artemether group was less than half that of the placebo recipients (3.4 versus 7.4 eggs/10ml urine, P<0.001). Heavy *S. haematobium* infections, microhaematuria and macrohamaturia, and the incidence of malaria parasitemia were all significantly lower in artemether patients. The authors concluded that artemether was active against *S haematobium* (N'Goran *et al*., 2003). Boulanger *et al* (2007) have also associated artesunate combination therapies with high cure rate of *S. haematobium* infection in Senegal. This author and colleagues investigated the efficacy of artesunate in the treatment of urinary schistosomiasis in Nigeria (Inyang-Etoh *et al.,* 2004)(Table 2). When the treated children were re-examined 4 weeks after the second dose of artesunate, 70.1% appeared egg- negative and were therefore considered cured. Post-treatment, the geometric mean egg count for the treated subjects who were not cured was significantly lower than the pre-treatment geometric mean egg count for all the treated subjects, with $\log^{10}$[(eggs/10 ml urine) +1] values of 0.9 versus 1.75 (t=4.45; P<0.05). The artesunate was well tolerated. The authors concluded that their observation of a therapeutic effect of artesunate against *S. haematobium* infection in Nigeria confirmed recent observations from Senegal. Furthermore, it would be more cost effective to treat *S. haematobium* infection in this setting with artesunate than with PZQ.

	Males	Females	All	X^2	P
Subjects Aged <10years					
No. Treated	11	21	32	NA	NA
No. and (%) cured	7(64)	15(71)	22(69)	0.2	>0.05
No and (%) without post-treatment haematuria	10(90)	18(86)	28(88)	1.66	>0.05
No and (%) with post-treatment haematuria	1(9)	3(14)	4(13)	0.09	>0.05
Subjects Aged>10 years					
No Treated	31	24	55	NA	NA
No and (%) cured	20(65)	19(79)	39(71)	1.40	>0.05
No and (%) without post-treatment haematuria	23(74)	20(83)	43(78)	0.65	>0.05
No and (%) with post-treatment haematuria	8(26)	4(17)	12(22)	0.66	>0.05

NA, Not Applicable
(Adopted from Inyang-Etoh, Ejezie, Useh *et a*l.,2004)

Table 2. The prevalences of haematuria post-treatment with artesunate and the frequencies of parasitological cure, split by age and gender.

Researchers have administered a combination of PZQ and artesunate on schistosomiasis infected subjects in a bid to derive a synergistic effect. While PZQ acts on the adult worms, artesunate acts on the immature stages of the worm. Borrmann *et al* (2001) investigated the efficacy and tolerability of artesunate, singly or in combination with PZQ, for the treatment of *S. haematobium* infections among 300 schoolchildren in Gabon. Of the children given PZQ + placebo, artesunate + placebo, artesunate + PZQ and placebo alone, 73%, 27%, 81% and 20% appeared cured, respectively. In summary, earlier findings of efficacy of artemisinin derivatives against *S. mansoni* and *S, japonicum* could not be confirmed against *S. haematobium* in the endemic focus. In a related study, conducted in two villages endemic for *S. haematobium* infection in Senegal, De Clercq *et al* (2002) reported that treatment with aretesunate alone gave egg count reduction rates that were high and almost as good as those obtained with PZQ (though the results obtained with PZQ were consistently better). Inyang-Etoh *et al* (2009) assessed the efficacy of a combination of PZQ and artesunate in the treatment of urinary schistosomiasis in Nigeria (Table 3). All treatment regimens were well tolerated. The cure rates were 72.7% in the PZQ plus placebo treated group and 70.5% in the artesunate plus placebo group, while the artesunate plus PZQ group had the highest cure rate (88.6%). The authors concluded that the treatment of urinary schistosomiasis with a combination of PZQ and artesunate is safe and more effective than treatment with either drug alone. The authors were however silent about the element of cost of the combination therapy. It is more expensive to use the combination than using either singly. The element of cost is very crucial in the choice of the appropriate drug to use as it should be affordable by the rural poor who are often afflicted by the disease.

Effect of treatment	PZQ Plus placebo (n=44)	Art Plus placebo (n=44)	Art plus PZQ (N=44)	PZQ without placebo (n=42)	Art without placebo (n=44)	Placebo plus placebo
No (%) cured	32(72.7)	31(70.5)	39(88.6)	31(73.8)	33(75)	4(9.1)
Mean ova reduction rate	79.3	72.3	93.6	76.7	52.1	111.5
Mean ova count before treatment ±SD	66.3±3.7	69.6±2.7	62.2±2.1	42.0±1.7	39.8±1.1	34.1±0.8
Mean ova count after treatment±SD	13.8±0.8	19.3±0.9	4.0±15.2	9.8±0.5	19.1±1.0	72±2.3
Mean haematuria before treatment ±SD	55.9±2.0	50.9±1.9	73.0±2.3	47.6±2.0	61.8±2.2	38.0±1.6
Mean haematuria after treatment ±SD	13.6±1.2	11.1±0.9	8.8±8.7	7.6±0.9	25.7±1.6	59.6±2.2
Mean Proteinuria before treatment±SD	190.9±	177.3±5.1	267.5±5.4	160.2±5.2	191.1±5.2	185.2±5.0
Mean Proteinuria after treatment±SD	65.7±3.3	85.5±3.9	4.0±15.2	24.8±1.9	102.1±4.4	213.9±5.3

(PZQ denotes Praziquantel, Art denotes Artesunate)
Source: Inyang-Etoh, Ejezie, Useh *et al*., 2009) etc

Table 3. Summary of therapeutic efficacy of PZQ and artesunate administered with placebo or in combination in Nigeria.

Artemisinins were originally snythesised for the treatment of malaria. There is a likelihood of a build up of resistance in malaria endemic areas where the drug is equally used in the treatment of schistosomiasis. It is worth noting that the combination therapy as it were has not given 100% efficacy so far in field studies. This is crucial as all the stages (immature stages and adult) of the parasite are targeted by the two drugs. This brings the issue of resistance once again to the fore. It might not be unreasonable to assume that the residuals not responding to the combination therapy might be pointing to a certain level of resistance. This would also imply that we be circumspect in deploying artesunate to treat schistosomiasis in areas endemic for malaria since it may enhance the development of resistance.

4. Molluscicidiing in schistosomiasis control

In the early days of schistosomiasis control in Egypt, a lot of emphasis was placed on molluciciding in a bid to interrupt transmission. Although, it is a component of an integrated method of control, it is not used currently in many endemic areas. Rather morbidity control in the short term using chemotherapy is more emphasized. Snail control is achieved by using chemical and plant molluscicides, biological predators and ecological methods. The main objectives of the use of molluscicides is to contribute, preferably in combination with chemotherapy and other feasible control measures, to significant reduction/control of schistosome transmission by cost-effective destruction of snail host populations and in particular, infected snails in selected habitats. The snail population density at transmission sites should be reduced by 95% (WHO, 1992).

The advantages to be derived from mollusciciding are:
1. Rapid interruption of transmission
2. Satisfactory cost efficiency
3. Non-desirability of community participation and utilization of simple application tools
4. Guaranteed safety margins to man and his domestic animals and plants
5. Easy integration with other pesticide control programme

The disadvantages to be derived include the following
1. The need for repeated applications, since eradication of snail host populations is rarely attainable
2. Requirement of technical discernment
3. Effect on schistosomal morbidity, even when snail control measures are efficient and in the absence of chemotherapy is delayed (WHO, 1992).

4.1 Qualities of a good molluscicide

There is currently no perfect molluscicide. It is not easy to develop a molluscicide that is likely to offer all the advantages outlined above. However, the basic requirements have been laid out by the WHO (1965). These include the following:
1. Toxicity to snails at low concentration
2. They must be safe to use in respect of acute and chronic mammalian toxicity
3. If they enter the food chain, they must not produce adverse effects
4. They must be stable in storage for 18 months or longer
5. Acceptable cost and ready availability
6. Particularly specific for snails
7. Low toxicity for non-biota
8. Diversity of formulations
9. Simple means of application and reliable means of measuring concentration in habitat

4.2 Assessment of effectiveness of some chemical molluscicides

A variety of compounds are molluscicidal. Among these include; penta chlorophenate, calcium, copper, lead and tin compounds which have been discarded because of toxicity. The molluscicidal property of copper, irrespective of the method of application has been less than satisfactory, especially in the presence of organic materials, certain kinds of dissolved solids, and at high PH values. Moreover, the cost effectiveness for copper sulphate, inspite of its low price, has been shown to be unacceptably high in comparison with that of niclosamide (McCullough, 1992).

4.2.1 Mode of action of some chemical molluscicides

Poisoning with molluscicides causes the snail either to retract into the shell and expel the haemolymph or to become swollen and remain extended from the shell. The later response is seen particularly with organotins and certain carbamates and suggests lost of water balance control (WHO, 1992). The water balance of gastropods is thought to be under neurosecretory control. N-tritymorpholine has been shown to reduce neurosecrtory control in *B. truncatus*, while long term exposure of the pulmonate, *Indoplanorbis exustus*, to barium chloride and copper sulphate also resulted in diminished neurosecretory activity. In addition, it has been shown that water flux through *B. glabrata* falls in the presence of a number of molluscicides at concentrations around their LC 50 values (McCullough, 1992). It may well be, therefore that molluscicides cause stress on the water-balance system and that

this alone is lethal to the snail, or that reduction of the normal water flow through the snail precipitates other functions similar to those describe above.

4.2.2 Effectiveness of some chemical molluscicides

In Japan, an inexpensive compound named B-2 (Sodium 2,5 dichloro-4-bromophenol) has been field tested in liquid and wettable powder formulations against the amphibious *Oncomelania nosophora* (Kajihara *et al*., 1979). Its residual concentration in soil decreased rapidly and its uptake in rice did not exceed 0.03 mg/L. Its toxicity has limited its wide spread use. The properties of some chemical molluscicides is presented on Table 4.

Niclosamide (marketed as bayluscide) is virtually the sole available molluscicide and in terms of effectiveness and completeness of evaluation. It is the molluscicide of choice (WHO, 1992). It has been a commercial success. The usual formulation of bayuscide (70% wettable powder and 25% emulsifiable concentrate) are both highly effective. In practical use, a concentration of 0.6-1 mg/L is recommended with exposure time of 8 hr (WHO, 1973) or 0.33 mg/L for 24 hr (Barnish and Prentice, 1981). Currently, there is no proven resistance to bayluscide. In a recent study, Dai *et al* (2010) showed that a novel suspension concentrate of niclosamide was toxic against *B. glabrata*. There was no differences in the effect of the suspension concentrate, the wettable powder of niclosamide and the ball-milled pure niclosamide against the adult snail.

The distribution of the snail hosts in their habitat is non-random, reflecting the where about of the food resources (e.g decaying vegetation, algae) and also physical features (e.g sandy/muddy substratum, water flow patterns) which attracts or repulse the mollusks (WHO, 1985). Snail host populations thus tend to be dynamic in space and time. These principles and the observations that low infection rates (e.g less than 1%) in snails may be associated with relatively high infection rates in a local community point to the need to identify potential transmission sites both geographically and seasonally, and to predict the

Physical properties	Niclosamide	Copper Sulphate	Sodium Penta Chlorophenat	Nicotinanilidae Candidate compound Group
Form of Technical material	Crystalline Solid	Crystalline solid	Crystalline Solid	Crystalline Solid
Solubility in Water	230mg/L PH Dependent	316g/L	330g/L	Not known
Toxicity				
Snail, LC 90	3-8	20-100	20-100	5
(mg/L x h)	2-4	50-100	3-300	20-50
Cercaria LC 90				
Formulations	700g/kg wetteble powder, 250/ml/L emulsion concentration	980g/kg pentahudrate crystals	750g/kg flaks 800g/kg pellets 800g/kg triquettes	Not yet formulated

Source: WHO (1973)

Table 4. Properties of Some Available and Candidate Molluscicides

habitats favoured by the snails (Anderson & May, 1979). Klumpp and Chu (1987) stated that in their experience in Iran, Egypt and Ghana, area wide molluscicide was expensive, wasteful, ecologically unsound and generally ineffective. They concluded on the other hand that focal molluscicide is a cost effective method in virtually all habitats. However, in endemic areas like the Nile Delta, it is unlikely that even focal/seasonal molluscicide will contribute significantly to a reduction in schistosomal transmission in the area as a whole. However, in certain affected communities where for example, population-based chemotherapy campaigns may have proved less satisfactory, focal/seasonal molluscicide, if carried out rigorously could probably play a useful, additional role in disease control.

The efficiency of focal molluscicide treatment against schistosomiasis re-infection in an irrigation scheme and in small dams area in Mali has been undertaken (Werler, 1989). The cost factor alone was sufficient to reject focal molluscicide treatment especially at the Plateau Dagon since transmission starts at the end of the rainy season if there is still water in the dams by then and slows down in the cool dry season. Laboratory evaluation of B-2 in the control of the snail intermediate host of schistosomiasis in South Africa has been conducted (Joubert and Precious, 1991). The authors noted that though B-2 has a marked potential for snail control in South Africa, that niclosamide remains the molluscicides of choice.

There are a lot of problems mitigating against the application of chemical molluscicides particularly in sub-Saharan Africa. It is not likely that community participation would be guaranteed for the purpose of focal molluscicide in endemic areas. The other problems are high illiteracy rate and cost of procurement of molluscicides.

4.3 Plant molluscicides

During the last two decades several excellent reviews on plant molluscicides have been published (Kloss and McCullough, 1982; Mott, 1987). Some major classes of natural products with recognized molluscicidal activity is presented on Table 5.

In several African countries, plant molluscicides have been identified and tested as a component part of an integrated control programme. Mkoji *et al* (1989) evaluated the molluscicidal activity of *Solanum aculeatum* berries against *Biomphalaria pfeifferi, Bulinus globosus* and *Lymnea natalensis* in Kenya. Fifty (50) mg powder L-1 of sun freeze-dried berries killed over 60% of all the tested snails while 25mg L of the sun dried material killed less than 60% of the test snails whereas similar concentrations of the freeze dried molluscicides produced 60-80% mortality in the snails under similar conditions. These findings suggest that *S. aculeatum* is a potent molluscicide and has the potential for the control of vectors of schistosomiasis and fascioliasis in Kenya. In Egypt, the molluscicidal properties of *Ambrosia maritina* on schistosome snail intermediate host has been assessed. This study was combined with the administration of PZQ. The authors concluded that *A. maritina* offers an alternative community participation approach whereby farmers could grow and apply the plant for themselves so that an area of any size could be treated in a short period of time. *A maritina* was able to reduce populations of *Biomphalaria alexandrina* significantly (Elsawy *et al*., 1989). Latex from the plant *Euphorbia splendens var hislopi*, also known as 'Crown of Christ' have been discovered to have molluscicidal effect on snails of the genus *Bulinus* and *Biomphalaria*. Schall *et al* (1998), obtained a 90% lethal impact on egg masses and embryos of these snails. This is one of the most potent molluscicides.

Class of Compoud	Plant	Family
Triterpenoid Saponins	*Phytolacea Dodecandra*	*Phytolaccacee*
	Hedra helix	*Araliaceace*
	Lonicera nigra	*Caprifoliaceace*
Spirostanol Saponins	*Cornus florids*	*Cornaceace*
	Balanites aegytiaca	*Balaniotaceae*
	Asparagus curillus	*Liliaceae*
Steroid glycoalkaloids	*Solanum mammosum*	*Solanaceae*
Diterpenes	*Wedelia scaberrima*	*Compositae*
	Baccharis trimera	*Compositae*
Sesquiterpenes	*Warburgia ugandensis*	*Canellaceae*
	Warburgia stuhlmannii	*Canellaceae*
	Ambrosia maritime	*Compositae*
	Podachaenium eminens	*Compositae*
Monoterpenes	*Genus Lippia*	*Verbenaceae*
Iridoids	*Olea europaea*	*Oleaceae*
Naphthoquinones	*Diospyres usambarensis*	*Ebenaceae*
Alkenyl phenols	*Anacardium occidentale*	*Anacardiaceae*
Chalcones	*Polygonum senegalense*	*Polygonaceae*
Flavonoids	*Baccharis trimera*	*Compositae*
Tannins	*Acacia nilotica*	*Leguminosae*

(Adopted from Marton and Hostettman, 1985)

Table 5. Major Classes of Natural Products with Recognised Molluscicides Activity

A major issue in the utilization of plants molluscicides is the acceptance and ownership of the initiative by community members. In the absence of this, cultural and religious factors may interplay negatively to hinder control. Community acceptance has been tested by different researchers in different settings. The processing and application of the soap berry plant (*Phytolacca dodecandra*) was tested in Ethiopia, where the plant is known as *endod*. Both occasional spraying and the use of *endod* soap for washing clothes were tested and it appeared that spraying would be the least labour- intensive method of control in that setting. Ndamba *et al* (1989) in a related study in Zimbabwe examined the knowledge, attitude and practice of the locals on both schistosomiasis and the soap berry plant. A large number of the participants accepted that schistosomiasis was a problem but none of them knew the role of snails in the transmission of infection. Although, they did not previously know of the plant as a molluscicides, a higher proportion of the people were willing to grow the plant after a brief explanation of it use.

It appears morbidity control of schistosomiasis anchored chiefly on population based chemotherapy has taken the centre stage in the organization of schistosomiasis control even with the acceptance of an integrated approach to control. The vigor thrown in by researchers in the early 1970s to 1990s in the search and evaluation of plant molluscicides has not been sustained.

4.4 Utilisation of competitor snails

Another approach to the elimination of snail hosts of schistosomiasis is the introduction of competitor snails in the habitat to the prey on the former. The South American snail, *Marisa*

cornuarieta is a noted prey of *B. glabrata* and this has been demonstrated in Puerto Rico (Muller, 1975). Similarly, the fresh water fish, *Astateodromes* is known to prey on mollusks. The Planorbid snail, *Helisoma duryi*, originally endemic in Florida, USA has been suggested as a biological competitor against the intermediate host snails of schistosomiasis. During the past three decades researchers have speculated on the possibility of using this particular snail as a biocontrol agent. Althought the results of some experiments indicated that *H. duryi* could control certain intermediate hosts under laboratory conditions and semi natural environment (Madsen, 1981), a number of field trials were either inconclusive or unsuccessful (Jordan, 1985).

Pointer *et al* (1989) have reported on the use of the parthenogenetic snails, *Thiara granifera* and *T. (Melanoides*) *tuberculara* to eliminate the intermediate host of *S mansoni- B. glabrata* in the Carribean area. These oriental snails are noted for their capacity to colonise rapidly and densely, many types of habitats while at the same time reducing and even eliminating populations of *Biomphalaria Spp*. In St Lucia, *B glabrata* was apparently eliminated from marshes and streams, 6 to 2 months after the introduction of the competitor. In Martinique, *T tuberculata* was introduced and in just less than 3 years, both *B. glabrata* and *B. straminea* were eliminated from the transmission sites. They concluded that, the Thiarid snails as competitors of pulmonates are favoured by the presence of permanent and stable habitat, preferably shallow, with emergent plants.

Taken alongside other measures, such as molluscicide and chemotherapy, the goal of eradication of schistosomiasis appears feasible and attainable in the long run. But some posers remain. What would likely be the long term impact between the interaction of schistosomes and competitor snails? Would they become vectors themselves someday? The utilization of this method would remain as a research tool for sometimes.

5. Ecological modification

Habitats can be made unsuitable for snails to exist by alternate flooding and drying of water channels, covering and lining of canals and filling in of marshy areas. Though these methods are likely to be permanently successful, they are expensive. Chenq (1971) reported that in Kiagsu and Chekiang provinces of China, the 10.5 million cases of schistosomiasis estimated to be present by 1955 were claimed to have been reduced by one third using ecological procedures in combination with the storage of night soil before use on the land and a three day treatment campaign with tartar emetic. The reduction in the water level, including complete drainage of the habitat, resulted in the death of the snails through desiccation (Boelee & Laamrani, 2004). Similarly, the ecological benefits to the snails such as, the presence of algae which served as their main source of food are removed. The lining of the canals with cement is another measure that may be adopted. It reduces the accumulation of silt and the growth of the vegetation; this in turn reduces the snail population at the site. Local participation is known to ensure the sustainability of this approach. In Morocco, the cost of control was reduced while the people took responsibility for their environment and health (Boelee & Laamrani, 2004). Strickland (1982) noted that such environmental management led to improved agricultural productivity in endemic areas.

5.1 Modification of the water-related activities of residents of an endemic area

Several studies have confirmed a strong link between the water related activities of residents of schistosome endemic communities and the prevalence and intensity of infection. In

Nigeria, Useh & Ejezie (1999b) showed that intensity of infection was more closely correlated with the number of water contacts (r=0.97) than with the total duration of exposure (r=0.77), emphasizing the importance of specific/multiple activities, and of the surface area of the body submerged in transmission. Although, the authors investigated four fresh water streams, one of them (Culvet) was identified as the main transmission point, with bathing/swimming and fishing as the main activities that predisposed people to infection (see Table 6).

Age (years)	No of Observations	No of Contacts	Mean No of Contacts/person-day	Total Duration (min)	Mean Duration/ Contact .day (min)	No and (%) of Subjects infected
5-9	479	489	1.20	4328	8.85	265(55.32)
10-14	559	588	1.05	6831	11.62	402(71.91)
15-19	385	442	1.15	7622	17.24	230(59.74)
20-24	298	318	1.07	7273	22.87	114(38.25)
25-29	172	188	1.09	5153	27.41	36(20.93)
30-39	158	162	1.03	4923	30.39	21(13.29)
>40	85	87	1.02	1095	12.59	8(9.41)
All	2136	2274	1.07	37225	16.37	1076(50.37)

(Adopted from Useh & Ejezie, 1999b)

Table 6. Frequency of water contacts, duration of exposure and prevalence of infection, by age of subjects

The application of the results of a study like this may change the attitude of the residents by encouraging them to avoid activities that expose them to infection. In a Zimbabwe study, Chandiwana and Woolhouse (1991) showed that water contact rates were related to age (highest in 8-10 years old) but not sex, with substantial variation unaccounted for by these variables. Their results provide strong quantitative support for control programmes aimed at heavily infected sites (eg focal mollusciciding) or at the minority of individuals making most water contact (e.g targeted chemotherapy).

The creation of habitats for intermediate hosts of many parasitic diseases including schistosomiasis can be avoided if there is collaboration by Government Departments charged with the supervision of building dams for agricultural purposes and hydro-electric power resources for energy supply. In the absence of this and proper channeling of canals, the government and the residents of such disease endemic areas would need any or combinations of the options outlined above to control the disease in question. The WHO (2000) defined three principles that are fundamental in dealing with the association between water resources development and human health:

- Equity. The benefits of water resources development are not disputed, but the uneven distribution of benefits (including health benefits) and of health risks to vulnerable groups, needs to be addressed in the planning, construction, and operation of such projects
- Economics. Negative health impacts of water resources development represent a hidden cost to the health sector whose resources are, as a rule, already over-stretched
- Sustainability. The economic return from investment in water resources development will suffer substantially from the ill health of local communities, with no sustainability at all in extreme case where dramatic health impacts force people to move away.

Where these principles are taken into consideration and actually put into practice water resources development would not create avenues for infection thereby sustaining the cycle of poverty and disease.

6. Sanitation and water supply

At the global level, the disability-adjusted life years (DALYs) from insufficient water, sanitation and hygiene (including contact with schistosome-infested waters) suggested that 4% of all deaths and 5.7% of the total disease burden can be attributed to these largely preventable conditions. However, with the emphasis placed on morbidity control of schistosomiasis using population-based chemotherapy, there is less focus on interventions related to safe water supply and sanitation, which in theory could contribute to controlling transmission of all helminths and many other infections (Prus *et al*., 2002). Bruun & Aagaard (2008) noted that the establishment of safe and adequate water supply and sanitation facilities at household and village levels has an effect on domestic utilization patterns, but the relationship to prevalence of schistosomiasis remain complex.

6.1 Sanitation

Sanitation is often considered as too expensive, but it is not known what proportion it would make up compared with sums spent on classical measures for the control of schistosomiasis. Schistosomiasis is transmitted through the contamination of water bodies with the eggs of the parasite via stool or urine. Considering the high reproductive potentials of the parasite, a single miracidium produces thousand of cercariae, thus a small proportion of human waste containing parasite eggs, reaching snail infested water is sufficient to maintain effective transmission in an area (Hotez et al., 2006). The provision of latrine facilities does not imply that they are always used by everybody as intended (Asaolu & Ofoezie, 2003). In a Brazilian town, where facilities were limited, Kvale (1981) showed that there was no significant difference in prevalence between people from households with septic tanks and people from households without such facilities. In a recent study in Brazil, Andrade *et al* (2009) showed that improved sanitation and income are associated with decreased rates of hospitalization for diarrhoea in infants. In a related study in Eygpt, el Katsha & Watt, (1997) showed that overall infection levels were higher in the village without a sewage system. When measured at household level, there was a statistical significant relationship between infection levels and the absence of sewerage connections, but in the better drained village, there was no similar significant correlation. Eventhough only a third of households were connected to the sewerage system in this village, the system had contributed to lowering the water table to the benefit of the general village environment.

Quite often sanitation is viewed and accepted as being very expensive. It has tremendous benefits not only in helping to control schistosomiasis but other endemic tropical diseases particularly those associated with fecal-oral route of transmission. When sanitation is accepted as the traditional way of life, the issue of cost would be grossly reduced. The Governments of endemic areas have the responsibility of the provision of sustained safe disposal of waste and the provision of simple public toilets. What is needed is to educate the people to desist from using faeces as fertilizer and enlightenment on their other actions which may predisposed them to infection

6.2 Water supply

The provision of alternative sources of safe water, such as piped water, wells, water tanks and laundry areas for domestic and recreational uses, contributed to effective reduction in the rate of transmission and re-infection (Kloos et al., 2008). As an experimental control measure to reduce the transmission of *S. mansoni*, an individual household water supply was provided in 400 houses in 5 rural settlements of the Riche Fond Valley, St Lucia (Jordan *et al.,* 1975). This population of about 2000 had previously been dependent for water on infected streams and rivers. Six other settlements in the valley, all provided with limited piped water from public standpipes, served as comparison area. After 2 years the incidence, prevalence and intensity of infection with *S. mansoni* were significantly lower in the household water supply area, whereas all these indices of infection had increased in the comparison area. The authors concluded that an adequate, reliable, and convenient supply of water can reduce the transmission of *S. mansoni* and should be considered as a control measure in other endemic areas. A comprehensive water delivery system consisting of a water outlet to each house, communal laundries, shower facilities, and play pools, coupled with health education were studied to determine the role they could play in the spread of schistosomiasis in St Lucia, West Indies (Jordan, 1988). After a 4 year period, the incidence of new *S mansoni* infections among children aged 2-5 years fell from 19.3% to 4.5% while over the same period in villages served by a standpipe system the incidence fell only slightly from 16.5%- 14%. In a related study in Cameroon, Ndamkou and Ratard (1990) investigated the role of sanitation, water supply and a health centre in the control of schistosomiasis. The authors noted that these parameters were effective in reducing the prevalence of schistosomiasis infection. In a different focus in Cameroon, Tchuem *et al* (2001) studied the impact of installation of a water pump on schistosomiasis transmission. They concluded that schistosomiasis focus evolve dynamically, and demonstrated that changes in water supply, in association with other actions such as repeated chemotherapy, may have a profound effect on disease transmission. A study in Kenya that installed community standpipes and a shower unit at the local school observed that the new water sources had a great influence on some villagers water contact behaviour and very little on the rest of the villagers (Noda *et al*., 1997). El Kholy *et al* (1989) investigated the effects of borehole wells on water use in a high prevalence area in Kenya, which showed no short-term effect on the transmission of *S. haematobium*, but a significant number of households changed to borehole water for drinking, cooking and dish washing.

A clean source of water would limit the possibility of contacting parasitic, virial and bacterial diseases. Although the importance of this is realized in the Developing world, the governments lack the financial and political will to embark on this. Where borehole water is provided, no mechanism is often in place for the maintenance of the facility. When it mal-functions, the residents resort to infested water bodies and become infected and the cycle of infection continues. There is also the need to take care of the recreational needs of the residents where piped water is available.

7. Health education

Health education is recommended as the entry point for initiating a control programme. Health education is that "aspect of health care directed towards promoting and reinforcing healthy behaviour through full participation of the individuals and communities concerned". It is a voluntary process that encourages people to make informed decisions to

improve and maintain their health (WHO, 1990). A systematical approach is required in order to properly educate the residents of schistosomiasis endemic areas to buy into the project. This is achieved through health educational planning which has the ten under listed components:

- A title
- A description of the target population,
- A statement of the problem or need
- A list of programme and educational objective
- A description of the means for community involvement
- An analysis of the factors that will promote or hinder programme success
- A list of appropriate health education strategies
- An outline of the resources available and the need for the programme
- A timetable for action
- A scheme for evaluation

A programme executed after the above consideration would yield excellent results.

Children are known to carry the greatest burden of schistosomiasis and soil transmitted infections. It is on this basis that the WHO recommended that the school system should be the focus in mounting intervention against these disorders. To meet this objective, Bundy and Guyatt (1996) summarized the key points to be taken into consideration when addressing health education in schools. It should be aimed to:

- Create awareness about the existence of the diseases, and build a bridge between scientific understanding of disease and children's perception of the disease in their every day lives
- Foster in children an understanding of what is healthy living, and what they can do to promote and practice this for themselves and their communities
- Give children practical skills in recognition of disease in themselves and their families, and in how to protect themselves and the community against such diseases,
- Encourage children's sense of responsibility for their own health and that of their families in the future.

Kamga *et al* (2003) assessed a health education strategy in the control of urinary schistosomiasis in Cameroon. School children given health education were found to be significantly less infected than those who had no health education. The investigators concluded that health education through the framework of a school could be adopted as a national policy for urinary schistosomiasis control programmes in tropical developing countries, planned with school children as full partners, provided that they received appropriate orientation. Assessing the knowledge, attitude and practice of residents of schistosome endemic areas about schistosomiasis and its control is critical in preventing infection. In Nigeria, Useh and Ejezie (1994) showed that 92% of respondents admitted knowledge of the disease (in their local language), although none of them knew about the aetiologic agent. About 82% of the respondents admitted procuring medication while 15.2% did not seek treatment of any kind. Perception of schistosomiasis and water- contact studies are very valuable in deploying control approaches.

8. Development of a schistosome vaccine

Despite the existence of effective chemotherapeutic agents, progress towards controlling schistosomiasis has been slow. Additionally, the possible development of resistance to PZQ

and other compounds, rapid re-infection and the overall economic cost, demand that other approaches be pursued (Coles *et al*., 1987). Butterworth *et al* (1992) argued that the aim of vaccination is to reduce morbidity. As in the various animal models, immunity in humans appears to be frequently incomplete. "Immune" adults often do become infected, but at lower intensities than "susceptible" children. Several investigations have confirmed that the severity of clinical disease is dependent on intensity of infection rather than simply the presence or absence of infection (Lehman *et al*.,1976 ; Chen and Mott, 1988) implying that even an incomplete immunity may be of considerable value.

An excellent review on the search for a schistosome vaccine was published not too long ago by Wilson and Coulson (2006). These authors rightly chronicled the search for the discovery of candidate vaccine molecules to have transited through mining crude extracts, monoclonal antibody targets, anti-idiotypes, expression library screening and immunogenicity. The early disappointment that was recorded with the vaccination of mice with crude worm extracts or purified components, followed by cercarial challenge (Sadun and Lin,1959 ; Murrell *et al*., 1975) and utilizing the idea of concomitant immunity (Smithers and Terry, 1969) were equally reviewed. Wilson and Coulson (2006) concluded that the sequencing of *S. mansoni* transriptome and genome and the development of proteomic and microarray technologies has drastically improved the possibilities for identiflying novel vaccine candidates, particularly proteins secreted from or exposed at the surface of schistosomula and adult worms. The parameters of an attenuated schistosome vaccine has been evaluated in the Olive Baboon (Kariuki *et al*., 2004). Five exposures of baboons to the attenuated schistosome vaccine gave greater protection than three exposures, but this attenuation was not sustained when challenge was delayed. Within the scope of the data collected, faecal and circulating antigen levels did not accurately predict the observed worm burdens. Levels of immunoglobulin G at challenge correlated best with protection, but there was little evidence of a recall response. In a related study in baboons, Coulson and Kariuki (2006) showed that neither a preceding infection, terminated by chemotherapy, nor an ongoing chronic infection affected the level of protection. Whilst IgM responses to vaccination or infection were short-lived, IgG responses rose with each successive exposure to vaccine.

The greatest hope for the discovery of a schistosome vaccine lies in Sh28GST which has already undergone Phases 1 and 2 human trials (Capron *et al.,* 2002). No adverse side effects were recorded in human recipients and high titres of antibodies were elicited in Phase 1 and phase 2 trials (Capron *et al*., 2005). The results of phase 3 human trials is being awaited. As noted by Curwen *et al* (2004) and Dillion *et al* (2006), current advances in post-genomic techniques are providing new avenues and hope to identify the secreted and surface-exposed antigens that mediate protection. The search must be sustained as vaccination is the most cost-effective and sustainable means of controlling endemic infectious diseases.

9. Conclusion

Schistosomiasis would continue to be relevant as one of the Neglected Tropical Diseases (NTDs) of public health significance in the tropics because of the attitude of the authorities of endemic countries in terms of mobilization of financial resources and political will to fight the disease. The hope of control still lies in an integrated approach. For now, the emphasis in the short term is based on chemotherapy with PZQ. The reduction in the price of PZQ means that millions of infected subjects can afford the drug. The artemisinins have performed well in relation to potency and price to PZQ in the control of all forms of

schistosomisasis and is recommended particularly in areas where malaria is not endemic. Although, clinical resistance to PZQ has not been scientifically proven, there is an urgent need to monitor its effectiveness closely as it is likely to remain the drug of choice for the foreseeable future.
The other elements that constitute the integrated approach such as the provision of piped water, health education and elimination of snail hosts of schistosomiasis have not been implemented with the same zeal as population based chemotherapy

10. Recommendation

In order to sustain the fight against schistosomisais, governments of disease endemic areas would have to increase funding to health including schistosomiais. A support programme that would further reduce the cost of PZQ with increase accessibility would go a long away. The activity of PZQ and artemisinins should be closely monitored both in vivo and in vitro for the development of resistance. The search for other potent anti-schistosome drugs should be pursued vigorously. Other key components like the provision of pipe borne water and health education should be put in place by the governments of endemic countries. There should be close collaboration between the Ministries of Health, Agriculture, Water Resources and Power Supply in the construction of Dams for water supply and provision of energy to avoid creating breeding grounds for vectors of diseases.

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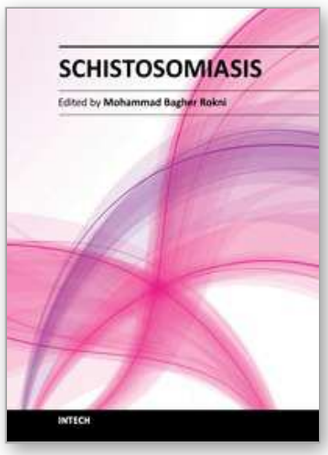

Schistosomiasis

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In the wake of the invitation by InTech, this book was written by a number of prominent researchers in the field. It is set to present a compendium of all necessary and up-to-date data to all who are interested. Schistosomiasis or blood fluke disease, also known as Bilharziasis, is a parasitic disease caused by helminths from a genus of trematodes entitled Schistosoma. It is a snail-borne trematode infection. The disease is among the Neglected Tropical Diseases, catalogued by the Global Plan to combat Neglected Tropical Diseases, 2008-2015 and is considered by the World Health Organization (WHO) to be the second most socioeconomically devastating parasitic disease, next to malaria. WHO demonstrates that schistosomiasis affects at least 200 million people worldwide, more than 700 million people live in endemic areas, and more than 200.000 deaths are reported annually. It leads to the loss of about 4.5 million disability-adjusted life years (DALYs).

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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