Treatment Effects and Integrated Morbidity Control of Schistosomiasis

Anthony Danso-Appiah

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Treatment Effects and Integrated Morbidity Control of Schistosomiasis

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Promotor:	Prof.dr.ir. J.D.F. Habbema
Overige leden:	Prof.dr. M.C.J.M. Sturkenboom Prof.dr. H.A. Verbrugh Prof.dr. J. Utzinger
Copromotor:	Dr. S.J. de Vlas

To my dear wife Joyce
and son Nana Owusu

Contents

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Chapter 2

Danso-Appiah A, De Vlas SJ. Interpreting low praziquantel cure rates of Schistosoma mansoni infections in Senegal. *Trends Parasitol*. 2002;18:125-9.

Chapter 3

Danso-Appiah A, Utzinger J, Liu J, Olliaro P. Drugs for treating urinary schistosomiasis. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000053. DOI: 10.1002/14651858.CD000053.pub2.

Chapter 4

Danso-Appiah A, Garner P, Olliaro PL, Utzinger J. Treatment of urinary schistosomiasis: methodological issues and research needs identified through a Cochrane systematic review. *Parasitology*. 2009;136:1-13.

Chapter 5

Danso-Appiah A, De Vlas SJ, Bosompem KM, Habbema JD. Determinants of health seeking behaviour for schistosomiasis-related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana. *Trop Med Int Health*. 2004;9:784-94.

Chapter 6

Danso-Appiah A, Stolk WA, Bosompem KM, Otchere J, Looman CNW, Habbema JDF, De Vlas SJ. Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana. (Submitted).

Chapter 7

De Vlas SJ, Danso-Appiah A, van der Werf MJ, Bosompem KM, Habbema JD. Quantitative evaluation of integrated schistosomiasis control: the example of passive case finding in Ghana. *Trop Med Int Health*. 2004;9:A16-21.

Chapter 1

General introduction

1.1 Human schistosomiasis

Distribution and burden of the disease

Schistosomiasis is caused by the blood fluke and leads to significant ill-health and economic burden. The disease is common in the tropics and subtropics and acquired through contact with freshwater bodies infested with the infective cercariae shed from the intermediate host snail. From a public health perspective, the three most important species are *Schistosoma mansoni* and *S. japonicum* (causing intestinal schistosomiasis) and *S. haematobium* (causing urinary schistosomiasis). Schistosomiasis is endemic in 76 countries and territories worldwide (Engels *et al*. 2002; Steinmann *et al*. 2006) with around 85% of the infections confined to sub-Saharan Africa (Savioli *et al.* 1997; Chitsulo *et al.* 2000). Schistosomiasis is largely confined to rural dwellings and exacerbates poverty (Hotez *et al*. 2008; Wang *et al*. 2008). In some areas of sub-Saharan Africa there is an overlap in distribution of *S. mansoni* and *S. haematobium* resulting in mixed infections (WHO 2002). This thesis focuses on urinary schistosomiasis due to *S. haematobium* and intestinal schistosomiasis due to *S. mansoni*.

Schistosomiasis is largely related to poverty, and efforts to alleviate poverty through development of water-related projects tend to increase transmission of the infection (Poda *et al*. 2004; Steinmann *et al*. 2006). Mostly children, women and farmers in poor rural areas who depend on water contact for recreational, domestic or occupational activities are affected. Peri-urban schistosomiasis is on the increase (Kloetzel *et al*. 1994; Chimbari & Chirundu 2003; Njiokou *et al.* 2004), and movement of displaced people from conflict zones has contributed to the spread of the disease to previously non-endemic areas (Chitsulo *et al.* 2000).

Schistosome life cycle and mode of transmission

Figure 1.1 gives a schematic representation of the life cycle of the schistosome. Man is the definitive host and some species of the Planorbid fresh water snails are the intermediate hosts in the transmission of the infection. Animals such as dogs, cats, rodents, pigs, horses and goats can serve as reservoirs, especially for *S. japonicum* (Combes 1990; Rey 1993; Duplantier & Séne 2000). Eggs of schistosomes are excreted through faeces (for intestinal schistosomiasis) or urine (for urinary schsitosomiasis) of infected people. In contact with water body and under suitable conditions, the eggs hatch to release larvae called miracidia, which swim to locate and penetrate specific snail intermediate hosts. In the snail, a schistosome passes through two developmental stages leading to the production of cercariae.

Immediately after their release into the water the cercariae swim vigorously to locate the human host. The infectivity potential of the cercariae increases rapidly after one hour and reaches saturation (plateau) nine hours post-emergence from the snail (Whitfield *et al.* 2003). Cercariae are phototropic and are shed into the water at mid-day to coincide with the time of most intense water contact activity such as swimming by children.

The cercariae penetrate the peripheral capillaries in the skin of the human host losing their tails in the process (Ryan 1994). However, recent evidence suggests that the cercariae penetrate the human host with the whole body (Whitfield *et al.* 2003). The cercariae (schistosomulae) migrate through venules, right chamber of the heart and lungs through the mesenteric arteries and the liver via the portal vein. Throughout the migratory processes, the parasite undergoes stages of transformation and maturation until the adult worms finally reside in venules in locations characteristic of the parasite species. *S. mansoni* worms are mostly located in the superior mesenteric veins draining the large intestine whilst *S. japonicum* worms are commonly found in the superior mesenteric veins draining the small intestine. *S. haematobium* are mostly located in the venous plexus of the urinary bladder but can also reside in the rectal venules.

Mature female schistosomes averaging 7-20 mm in length and longer than their male counterparts pair-up with the males and live in the gynaecophoric canal of the males where they mate and produce large numbers of eggs. On average, adult worm pair lives for 3-5 years, but some can live up to 30 years (Warren 1982; Arnon 1990; Hornstein *et al*. 1990) with reproduction potential of one schistosome pair estimated to be up to 600 billion schistosomes (Gryseels *et al*. 2006). schistosome eggs have characteristic spines and must traverse the lumen of the intestine (*S. mansoni* and *S. japonicum*) and bladder and ureters (*S. haematobium*) for excretion with faeces or urine, respectively. A considerable number of the eggs become trapped in the tissues in the process of elimination from the body.

Pathology and morbidity

The schistosome worms themselves do not cause disease. Eggs trapped in the tissues cause the disease by initiating immune-induced inflammatory reactions. Within few hours after infection a rash or itchy skin may occur at the site of penetration. Fever, chills, cough, muscle aches, abdominal pain, diarrhea, hepatospenomegaly and eosinophilia may begin within 1-2 months of infection. This is known as Katayama's syndrome and mainly occurs in individuals who do not have protective immunity (Zuidema 1981; Istre *et al*. 1984). Occasionally, there is central nervous system involvement with fatal outcomes (Naus *et al*. 2003). The severity of disease depends

upon the intensity of infection and most individuals with few schistosome worms, especially adults, remain asymptomatic whilst about 80% of infected children show early symptoms and signs of disease (Mott *et al*. 1983; Gryseels & Polderman 1987; Olds & Dasarathy 2000). The World Health Organisation estimates that up to 120 million people show symptoms of schistosomiasis worldwide (WHO 2002). Signs and symptoms related to schistosomiasis have been summarized in Table 1.1.

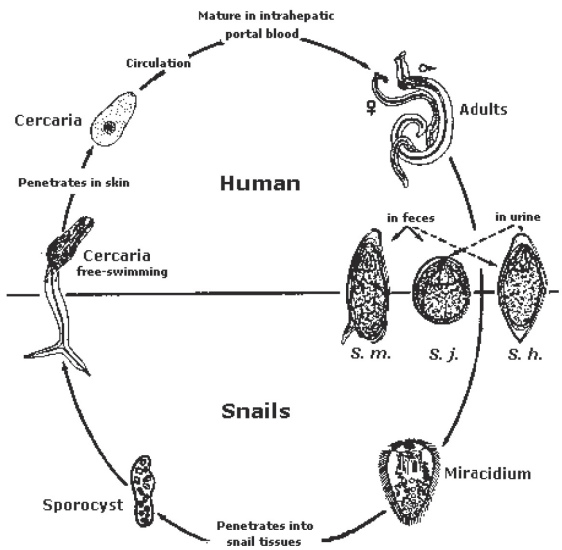

Figure 1.1 Schistosome life cycle and mode of transmission. Source: courtesy of the CDC web site: http://www.dpd.cdc.gov/dpdx/HTL/Schistosomiasis.htm

The early manifestation of *S. mansoni* infections are in two forms; mostly intestinal, but also hepatosplenic. Intestinal schistosomiasis is caused by a cellular granulomatous inflammation formed around eggs trapped in the tissues and gives rise to diarrhea, blood in stool or abdominal pain. The inflammatory reactions in the liver lead to hepatosplenomegaly. The small intestine is the segment where large numbers of eggs are deposited but the large intestine usually show severe forms of lesions. Colonic polyps have been seen mostly in patients from Egypt (Cheever 1978, Cheever *et al*. 1978).

Table 1.1 Schistosomiasis-related signs and symptoms following an established infection.

Stage of symptom	*S. mansoni*	*S. haematobium*	Both (non-specific)
Early‡	– Diarrhoea – Blood in stool – Bloody diarrhoea – Abdominal pain – Hepatomegaly – Splenomegaly	– Haematuria – Dysuria	– Anaemia – Fatigue
Late-stage†	– Colonic polyps – Cirrhosis of the liver – Pipe stem portal fibrosis – Hepato-splenomegaly – Portal hypertension – Varicose veins – Haematemesis – Hemorrhage from – rupturing varicose veins – Haemorrhagic shock	*Functional (localised)* – Bladder wall thickening Bladder wall calcification – Bladder stones – Squamous cell carcinoma *Complications* – Secondary bacterial infection – Bladder abnormal pyelon dilation – Anuria – Hydroureter – Distal ureter hydrone-phrosis – Kidney failure	– Anaemia – Fatigue – Nutritional deficiencies – Poor growth – Memory loss – Slower Reaction time – Lower Scores in cognitive ability

‡ May occur a few weeks or months after the infection

† Insidious and may take a long time depending on the intensity of infection

Haematuria = Blood in urine; Dysuria = Painful urination; Hepatomegaly = Enlargement of the liver; Splenomegaly = Enlargement of the spleen; Anuria = No urine excretion.

The hepatosplenic form usually manifests within a couple of months for heavy infections, but mostly it develops many years after exposure to the infection. This stage of the disease is a consequence of fibrotic reaction around the egg in the liver, and an associated enlargement of the spleen (splenomegaly). Fibrosis in the granuloma leads to a so-called “Pipe stem Portal Fibrosis” as the inflammatory response spreads to portal blood vessels proximal to pre-sinusoidal vessels containing trapped eggs. The fibrotic reactions lead to cirrhosis of the liver which in turn gives rise to portal hypertension that inhibits blood flow through the liver to give rise to ascites. The portal hypertension eventually leads to enlargement of hepatic arteries, which then send out new collateral blood vessels. The associated varicose veins may rupture resulting in massive blood loss, haemorrhagic shock and death. The patient may also suffer repeated episodes of variceal bleeding before finally dying from it.

For *S. haematobium*, blood in urine (haematuria) and painful urination (dysuria) are the main early symptoms of the disease. However, it has been suggested that even in the early stages of the infection, parasite-induced pathological changes of the bladder and abnormal pyelon dilation of at least one of the kidneys are common in children (Brouwer *et al*. 2003). This suggests that pathology may develop much earlier following the infection than initially thought.

Tissue damage caused by trapped eggs can lead to diffused or localized wall thickening of the bladder and distal ureter hydronephrosis or hydroureter, which may eventually lead to kidney failure (Kardorff & Doehring 2001; WHO 2002). A recent review points out that bladder carcinoma is the 7th most common cancer worldwide in men and that the highest incidence rate among men is found in Egypt (Murta-Nascimento *et al*. 2007), which may be related to *S. haematobium* infection and morbidity (Jordan 2000).

Late stage complications are insidious and lead to structural changes or damage allowing intravascular shift in location of the worms. The superior mesenteric veins have numerous anastomoses with the veins draining the internal genital organs and the vulval area towards the inferior vena cava. The structural damage to valves allows unrestricted migration of worms to the genital organs where they deposit eggs to initiate genital organ pathology (van Raalte *et al*. 1981; Arora *et al*. 1986; Smith & Christie 1986; Feldmeier *et al*. 1998; Poggensee & Feldmeier 2001). There are also communications between the spermatic ducts with the superior and inferior mesenteric veins allowing eggs to move into the semen (Arean 1956). In females the linkage between the ovarian and uterine plexus through anastomoses allows free movement of eggs to the cervix and the vagina thereby affecting the female reproductive organs (Arean 1956; Camara 1959).

Public health impact of the disease

Parasitic worms may be the commonest cause of chronic infection in humans. In many low income countries it is common to be infected repeatedly (Woolhouse *et al*. 1991). Recent global estimates indicate that more than a quarter of the world's population is infected with one or more of the most common geohelminthic parasites (WHO 2002). Around 780 million people are at risk of schistosomiasis and more than 200 million are infected causing an annual loss of 4.5 million disability-adjusted life years (Hotez *et al*. 2006; Steinmann *et al*. 2006). Among the infected people an estimated 120 million are symptomatic and 20 million suffering from severe long-term consequence of the disease (WHO 2002). *S. haematobium* and *S. mansoni* infection alone may contribute to the deaths of more than a quarter of a million people a year from schistosomiasis-related complications (van der Werf *et al.* 2003). Female and male genital schistosomiasis reduces fertility and may promote the spread of HIV/AIDS (Leutscher *et al*. 2000; Poggensee & Feldmeier 2001).

A major problem is that deaths resulting from long term consequence of schistosomiasis are rarely acknowledged to be due to schistosomiasis as there is hardly any recognition of the link between infection in early life and later development of severe disease. The social and economic burden of schistosomiasis is thought to be even greater (WHO 2002). Recent studies have suggested that the burden due to schistosomiasis has been significantly underestimated (King *et al.* 2005; Engels & Savioli 2006), and that the design of the DALY has inherent flaws that result in a systematic undervaluation of the importance of chronic diseases, like many of the so-called neglected tropical diseases, including schistosomiasis (King *et al.* 2008). Further research has suggested far reaching implications of the association between heavy infection in schoolchildren and short-term memory loss, slower reaction time, lower scores in some tests of cognitive ability and poor growth (Stephenson 1993; Nokes *et al*. 1999; PCD 1999; Jukes *et al*. 2002; WHO 2002). Iron deficiency anaemia and other nutritional deficiencies have also been linked with heavy infection (Awasthi *et al*. 2003) whilst data from Egypt, Sudan and Brazil have shown a consistent link of absenteeism from infected school children and reduced work capacity of rural inhabitants due to lethargy caused by schistosomiasis (WHO 2002).

1.2 Diagnosis and control

Detection of infection and diagnosis of the disease

Parasitological diagnosis by microscopy of urine for parasite eggs is the most practical and widely used method for identifying infected individuals (Hassan *et al*. 1994). For *S. mansoni* and *S. japonicum* the infection is diagnosed and quantified using the Kato-Katz technique by examining single or multiple stool specimens (20-50 mg per slide). For urinary schistosomiasis, the egg count is quantified using a Nucleopore membrane of a standard 10 ml volume of urine. Reagent strips for detecting blood in the urine are also used, but this technique is unable to quantify the infection. Field methods used for detecting *Schistosoma* infections miss a large proportion of the infections and prevalences are far under-estimated, with important consequences for control and research (De Vlas *et al*. 1992; Utzinger *et al*. 2001). Egg output can be influenced by several factors, such as day-to-day variations in egg output, seasonal variations and environmental conditions (Braun-Munzinger & Southgate 1992). Therefore negative results following microscopic examination of a single stool or urine specimen are not reliable (De Vlas *et al*. 1992; Enk *et al*. 2008). Generally, measurement of prevalence and intensity of infection by egg count has shortcomings (Gryseels & De Vlas 1996; De Vlas *et al*. 1997; Utzinger *et al*. 2001). Rectal biopsy

for all species and biopsy of the bladder for *S. haematobium* are more sensitive than microscopy and occasionally done when repeated stool or urine examinations are negative for schistosome eggs. However, biopsies are invasive thereby limiting their wide application (Allan 2001).

Recently, monoclonal antibody-based diagnosis of the disease by detecting schistosome-specific by-products have been developed and field-tested (De Jonge *et al*. 1989; Deelder *et al*. 1994; De De Kremsner *et al*. 1994; Bosompem *et al*. 1996, 1997) with some promising results (Bosompem *et al*. 1996, 1997, 2004; Polman *et al*. 2001, 2002). However, large scale application of antibody-based diagnosis is limited at the moment (WHO 2002).

Ultrasound was introduced in the 1970s to detect schistosomal pathology both at hospital and field level (Mohamed-Ali *et al*. 1991; Doehring-Schwerdtfeger *et al*. 1992; Hatz 2001). It is a safe, rapid, non-invasive and relatively inexpensive technique for assessing infection associated pathology (Hatz *et al*. 1990).

Clinically, intestinal schistosomiasis is diagnosed on the basis of presence of blood in stool, diarrhoea, abdominal pain or hepato-splenomegaly. However, these symptoms are neither sensitive nor specific (Gryseels *et al*. 1992), and clinical diagnosis is only suggestive of the disease. For urinary schistosomiasis clinical diagnosis is based on terminal blood after urination or by inspecting the urine for haematuria. Diagnosis based on presence of blood in urine is reliable in children but this tends to be less reliable in adults (Red Urine Study Group 1995; Ansell *et al*. 1997). This is because blood in the urine of an adult may be due to causes other than urinary schistosomiasis such as sexually transmitted diseases.

Control strategies

Schistosomiasis control programmes have the primary objective of reducing or eliminating illness. Four main control strategies have been employed with varying success: 1) *Health education* to promote good hygiene and sanitation, especially among school-aged children and caregivers, and discourage practices such as bathing in streams and indiscriminate disposal of refuse that may entail risk of infection. The ultimate goal is to decrease the number of eggs reaching and contaminating the environment, particularly fresh water bodies. However, the long-term impact of health education on the transmission of schistosomiasis is questionable (Kloos 1995; Sow *et al*. 2003); 2) *Water supply and sanitation* to reduce frequency of water contact associated with domestic-related activities such as fetching water from streams for drinking, washing clothing or bathing in streams; 3) *Control of the intermediate host snail* by treating infested water bodies with molluscicide to destroy the intermediate host snail. Also, water and environmental management such as removal of vegetation

around banks of streams and lining irrigation canals with concrete slabs (Steinmann *et al*. 2006).The important role environmental management as part of an integrated control approach has played in conquering schistosomiasis japonica in China has been emphasized (Utzinger *et al*. 2005); and 4) *Morbidity control by chemotherapy of the human population* aimed at reducing burden of the disease thereby transmission of the infection.

Chemotherapy

Past control measures focused largely on reducing or interrupting transmission of the infection, but such measures have not been sustainable due to high cost and operational difficulties (WHO 2002). The advent of inexpensive, efficacious and safe drugs has made chemotherapy the most cost-effective strategy thus shifting control emphasis to morbidity control (WHO 1993). In areas with high endemicities, the current emphasis of control is to reduce the burden of disease whereas the focus is to interrupt transmission of the infection in low endemicity areas (WHO 2002). Intensity of infection is highest in children and adolescents. Therefore, chemotherapy is targeted especially to school-aged children (Magnussen *et al*. 2001; WHO 2002; Savioli *et al*. 2004). The assumption is that reducing the worm burden in childhood will prevent most long-term complications occurring later in adulthood.

A variety of drugs such as the antimonials, niridazole, lucanthone, hycanthone, cyclosporin A, levamisole and oltipraz have been used or tried for the treatment of schistosomiasis but abandoned because of poor effect or adverse events (For extensive review see Cioli *et al*. 1995). Three main drugs – oxamniquine, metrifonate and praziquantel – have been used extensively for the control of schistosomiasis (Cioli *et al*. 1995; Utzinger & Keiser 2004).

Metrifonate is an effective antischistosomal drug introduced in 1952 as an insecticide (Lorenz 1955) and early 1960s as a drug for humans (Snellen 1981). The drug given at a standard dose of 7.5-10 mg/kg 3 times at 14-day intervals has been used extensively and is mostly well tolerated (Forsyth 1966; Davis & Bailey 1969; Rugemalila & Eyakuze 1981; Feldmeier & Doehring 1987). It is one of a few drugs where clinical trials were carried out even before any detailed testing in animals was initiated (Aldridge & Holmstedt 1981). Adverse events are mainly as a result of cholinergic stimulation – fatigue, muscular weakness, abdominal colic, diarrhoea, nausea, vomiting and bronchospasm.

Oxamniquine is related to hycanthone and effective against only *S. mansoni*. It is practically without effect against *S. haematobium* (Yarinsky 1972; Foster & Cheetham 1973; Cioli *et al*. 1995). Following its introduction in clinical practice in the early 1970s it has been used widely with good effect. For example, in Brazil more than 12 million doses have been administered in the frame work of the national schistosomiasis

control programme (Katz & Coelho 2008). It works by causing the worms to shift from the mesenteric veins to the liver where the male worms are retained and destroyed. The female worms return to the mesentery, but can no longer produce eggs. Lower doses are given in South America, the Caribbean islands, and West Africa; a single dose of 15 mg/kg for adult patients and 20 mg/kg for children. In other countries of Africa and the Arabian Peninsula, higher doses are given, the total dose varying from 30 mg/kg to 60 mg/kg (Foster 1987). Side effects are mild and transient and include; dizziness with or without drowsiness, headache and gastrointestinal effects such as nausea, vomiting, and diarrhoea. Differences in the susceptibility of parasites to the drug seem to account for the variation in dosage.

Praziquantel (PZQ) is a broad spectrum antischistosomal drug effective against all the *Schistosoma* species. It is administered orally at a standard single dose of 40 mg/kg body weight and well-tolerated. Side effects are mild and transient and mostly related to the gastrointestinal tract: abdominal pain, nausea, vomiting, anorexia and diarrhoea. Praziquantel is refractory against immature worms (Sabah *et al*. 1986).

Current status of antischistosomal drugs and vaccines

In the late 1990s, metrifonate was withdrawn from the World Health Organization (WHO) model list of essential medicines because it was considered clinically, economically and operationally inferior to PZQ as it is only active against *S. haematobium*, requires multiple administrations, and hence less convenient in large-scale control programmes (Feldmeier & Chitsulo 1999). The application of oxamniquine has declined considerably and in areas where it was formally used as the drug of choice it is being replaced with PZQ (Cioli 2000; Beck *et al*. 2001; Reich & Fenwick 2001; Utzinger & Keiser 2004). At present, there is no effective and acceptable antischistosomal vaccine (Utzinger *et al*. 2007; Bergquist *et al*. 2008), and the sharp fall in price of PZQ has promoted large-scale morbidity control programmes (Fenwick *et al*. 2003, 2006). Ironically, this also stalled investments in the discovery and development of alternative control measures, such as other drugs, vaccines and diagnostics (Utzinger *et al*. 2007). Since the early mellinium, PZQ use has increased considerably after the 54th World Health Assembly resolved that at least 75% of school-aged children and other high-risk groups should be treated with PZQ in high burden areas by 2010 (WHO 2002). School-aged children in selected African countries have received multiple doses of PZQ since the launch of the 'Schistosomiasis Control Initiative' in 2003 (Fenwick *et al*. 2006).

At present, there is no effective and acceptable antischistosomal vaccine (Gryseels 2000; Fenwick *et al*. 2006), whilst the artemisinins which have shown anti-

schistosomal activity against immature schistosomes refractory to PZQ (Utzinger *et al*. 2003, 2007) did not give promising results in a field trial (Borrmann *et al*. 2001). Praziquantel remains the only antischistosomal drug on the WHO Model List of Essential Medicines for the control of schistosomiasis and thus vulnerable to the development of resistance. There have not been recent reviews on the potentials of metrifonate and oxamniquine as alternative to PZQ, or to replace PZQ in the event of resistance.

1.3 Praziquantel

Action

Praziquantel was discovered in the early 1970s and introduced in clinical practice in the early 1980s under the trade name Biltricide. When administered it is rapidly taken up by the schistosomes which are incapable of transforming it metabolically as opposed to the human host who readily metabolizes PZQ to an inactive form which is excreted through the urine (Andrews 1981). The primary mode of action is an instant contraction of the muscle cell membrane of the schistosome worms followed by spastic paralysis that leads to loss of attachment to the endothelium of veins of the host. Subsequently, the paralysed worms are transported in the vascular system from the mesenteric veins to the liver for destruction (Andrews 1981; Mehlhorn *et al*. 1981).

Praziquantel has been used widely with good effect parasitologically, and on morbidity (Barakat *et al*. 1995; Gryseels & Nkulikyinka 1989; King *et al*. 1990; El Malatawy *et al*. 1992; Hagan *et al*. 2004; King *et al*. 2005). The drug also has good safety profile for short and long-term use (Frohberg & Schulze-Schencking 1981; Frohberg 1984), and in pregnancy and lactation (WHO 2002; Friedman *et al*. 2007; Tweyongyere *et al*. 2009). Usually population treatment produces cure rate of over 70%. However, efficacy of treatment is influenced by a number of factors such as the epidemiological situation and the prevailing ecological conditions (Gryseels *et al*. 1992). Cure rates decrease with pre-treatment intensity of infection, number of prepatent infections, diagnostic sensitivity and age of the treated individuals. Poor drug quality and poor patient compliance may also negatively impact on effectiveness of treatment. Even, optimal timing at which treatment is evaluated affects the outcome of treatment (Scherrer *et al*. 2009). Even though re-infection may occur soon after treatment, particularly in children, pathology is resolved or at least its development is delayed (WHO 1993; Mohamed-Ali *et al*. 1991; Doehring-Schwerdtfeger *et al*. 1992).

Properties, production and distribution

Praziquantel comes as a long tablet containing 600 mg of active ingredient with two or three grooves for ease of divided doses. In China, it is distributed in pills containing 200 mg of the active ingredient whilst some manufactures provide syrup formulation containing 600 mg/5ml (eg Epiquentel from EIPICO). The shelf life is normally four years in temperate climates and three years in hot humid environments. Following oral administration the drug is rapidly and almost completely absorbed, with reasonable amounts appearing in the blood within 15 minutes (Valencia *et al*. 1994). Peak concentration is attained 1-2 hours after treatment. Thereafter, the drug undergoes a pronounced liver first pass metabolism with rapid disappearance from the circulation at a plasma half-life of 1-3 hours. About 80% of the drug is cleared within 24 hours of treatment primarily through urine (Cioli *et al*. 1995).

In 1980s further developments were initiated to produce new brands and generic forms such as distocide by Shin Poong (Korea), and in the late 1980s Bilharzid in Egypt under license from Shin Poong and Prazitel (Kenya). Other countries such as the Netherlands and Malta also followed with new brands (Cioli & Pica-Mattoccia 2003). The variety of brands in distribution raised concern about drug quality, but analyses of tablets from different manufacturers collected at the user level in endemic countries showed that the active ingredient, purity, disintegration and dissolution were within the standard requirement (Doenhoff *et al*. 2000; Appleton & Mbaye 2001; Sulaiman *et al*. 2001).

Praziquantel resistance

Drug resistance is defined as genetically transmitted loss of susceptibility to a drug in a parasite that was previously sensitive to the appropriate therapeutic dose (WHO 1996). In the early 1990s, praziquantel treatment in northern Senegal resulted in cure rate lower than normal: 18% after 12 weeks of follow-up (Gryseels *et al*. 1994; Stelma *et al*. 1995). One explanation of the unusually low cure rate was attributed to the emergence of resistance to praziquantel (Editorial 1992; Brown 1994). Subsequent studies in the same area showed cure rates of 31–38% after 6 weeks of follow-up (Gryseels *et al*. 1994; Van Lieshout *et al*. 1999). However, a normal cure rate was achieved with oxamniquine (Stelma *et al*. 1997). Further studies in Senegal up to the late 1990s kept on showing cure rates lower than usual (Guisse *et al*. 1997; Picquet *et al*. 1998; De Clercq *et al*. 1999; Ernould *et al*. 1999).

Meanwhile, analysis of *S. mansoni* strains obtained from patients in Egypt and Senegal treated with praziquantel but not cured yielded isolates tolerant to higher doses of the drug. In mice, *S. mansoni* strains from northern Senegal produced isolates less sensitive to praziquantel (Fallon *et al*. 1995). It was suggested that

reduced efficacy of PZQ in the Senegalese isolate was the result of tolerance rather than resistance because the focus had not been subjected to previous drug pressure (Gryseels *et al*. 1994; Fallon *et al*. 1996). Other reasons for the reduced effectiveness of PZQ in Senegal were attributed to the very high intensity of infection, presence of immature worms less susceptible to PZQ and acquisition of a large number of new infections immediately after treatment. Clearly, there is a need to compare cure rates in Senegal to other countries in a systematic way to rule out poor performance of PZQ.

1.4 Integrated control within the regular health service

Vertical control

Schistosomiasis control measures implemented before the 1970s when effective antischistosomal drugs were not available focused mainly on interrupting transmission of the infection by application of molluscide to target the intermediate host snails (Sturrock 2001). For example, in the mid 1960s the creation of the Volta Lake in Ghana led to rapid spread of schistosomiasis but control was based purely on application of molluscide to kill the intermediate host snails (Chu 1978). Chemical control proved to be very expensive, impractical and raises a lot operational and health concerns (Chu 1978; Sturrock 2001).

The 1970- 1980s marked the turning point in schistosomiasis control when effective drugs were developed shifting control emphasis to chemotherapy of the human host (Cioli *et al.* 1995). The initial assumption was that treating individuals harbouring large number of worms would reduce transmission of the infection. However, the high cost of drugs at that time made universal control of schistosomiasis not possible. Therefore, experts suggested that selective treatment ie identification of high prevalence communities, screening the people and treating those identified to have the infection would be more cost-effective (WHO 1985). Although the short-term results with selective treatment, mainly through vertical programmes, undoubtedly were good, the long term impact was disappointing due to lack of financial sustainability. Availability of drugs and treatment depended on the duration of the programme mostly supported by external donors (Gryseels 1989). Individuals treated would become infected again after a programme has been completed and the financial support and expertise withdrawn (WHO 2002).

Recognising the lack of sustainability of vertical programmes, the World Health Organization in association with the ministries of health of several endemic countries, mostly from Africa, met in 1983 and launched a programme to assess

viable schistosomiasis control strategies (WHO 1985). Subsequently, in 1984 the WHO Expert Committee on the Control of Schistosomiasis endorsed a strategy for morbidity control with chemotherapy as key component (WHO 1985). The aim has been to reduce the burden of the disease and prevent the development of chronic morbidity by regular treatment of individuals manifesting signs and symptoms of the disease or having high egg counts as identified through population surveys. Within this approach the standard single 40 mg/kg dose of praziquantel has been the treatment of choice recommended by the WHO (WHO 1985, 2002).

Many foreign donor agencies have supported or implemented several small-to-large scale vertical control programmes, especially in sub-Saharan Africa (WHO 1993, 1998). Through the vertical approach, treatment has also been targeted to school children (The Partnership for Child Development 1999). Nevertheless, the vertical approach has not been sustainable (Kumar & Gryseels 1994), mainly due to lack of involvement of local people and utilization of existing structures to ensure continuity of control after the foreign experts have left (WHO 2002).

The horizontal approach

In 1991 the WHO Expert Committee reviewed the control strategy and concluded that morbidity control was feasible and effective (WHO 1993). However, the committee identified that for a sustainable control there should be a prominent role of the existing health service- "horizontal approach". The objective has been to provide treatment to cases of schistosomiasis-related symptoms that self report to a clinic or hospital-passive case finding. The assumption is that if signs and symptoms are recognised early by the patients themselves and seek the appropriate treatment, most severe forms of pathology that develop later can be prevented.

The horizontal approach looks promising in the sense that it is based on the primary health care concept which has already been embraced and implemented in many endemic countries in Africa. Other reasons why the horizontal approach shows potential for success are: 1) the cost of antischistosomal drugs has fallen sharply to the extent that treatment has become more affordable for national health budgets or individuals who needs it; 2) control within the regular health service will strengthen the local health services, 3) related activities can be easily combined, for example the control of schistosomiasis can be combined with other helminthiases of public health relevance such as soil transmitted helminthes or malaria as these diseases tend to occur at the same time in an individual (WHO 1998) and, 4) many parts of Africa where the highest burden of the disease is concentrated did not benefit from the donor-supported vertical control programmes (WHO 1998).

In December 1998, programme managers, scientist and public health experts met in Geneva in an informal consultation to review schistosomiasis control strategies and reset the agenda for future control activities (WHO 1998). The expert recognized the leading role the World Health Organization during the 1970-1980s in developing control strategies but acknowledged that in sub-Saharan Africa only a few countries had ongoing control programmes (WHO 1998). It was noted that praziquantel was often not available at the peripheral health facilities where it is needed most because it was too expensive. At the same time major challenges were identified; 1) how to make praziquantel widely available to communities where the drug is needed most at an affordable cost; 2) how to organize and finance the distribution of praziquantel to those who need it in a sustainable way; and 3) how to adjust control measures to the varying distribution pattern and public health relevance of schistosomiasis in different communities.

Also, it was felt that drug supply from a strong centralised purchasing system with distribution through the existing health services according to local needs would be greatly facilitated by decentralised planning and implementation of control strategies (WHO 1998). Certainly, this will encourage acceptability, efficiency and sustainability. However, it is unknown whether availability of praziquantel alone in health facilities itself would significantly lead to an improved rate of hospital visit. The expert committee also recommended that schistosomiasis control should aim at building local capacity and strengthen existing health services with emphasis on integration of control and decentralisation of decision-making and delivery. A decentralized control is very important in that schistosomiasis is a focal problem and often its importance is diluted when control activities are planned and managed at the national level (WHO 2002).

Since 2000 praziquantel use has increased considerably especially in countries selected as part of the "Schistosomiasis Control Initiative' which was launched in 2003 (Colley *et al.* 2001; WHO 2002; Hagan *et al.* 2004). The sharp fall in price of praziquantel and effort by most countries in sub-Saharan Africa to restructure their health systems may be positive for integrated control by passive case finding. Undoubtedly, availability of praziquantel in peripheral health facilities may encourage patients to visit the facilities.

The prerequisites for successful integrated schistosomiasis control through passive case finding are appropriate health care seeking behaviour, adequate performance of health professionals, good referral strategies and availability of praziquantel (Figure 1.2). As pathology is strongly related to intensity and duration of infection, treating early cases may also prevent most severe complications that develop many years after the infection (WHO 2002). Schistosomiasis has been

controlled in many regions and longer poses a major public health problem in Japan, China, Iran, Laos, Mauritius, Morocco, Saudi Arabia, Tunisia, the endemic Caribbean islands, parts of Brazil and Venezuela. Thus, with an adequate health infrastructure, resources and political will, the available tools for the control of schistosomiasis can be used to good effect as control is far more effective when placed in the context of a general health system (WHO 2002). Although the integration process is slow the horizontal approach is now becoming an integral part of health care at the community level.

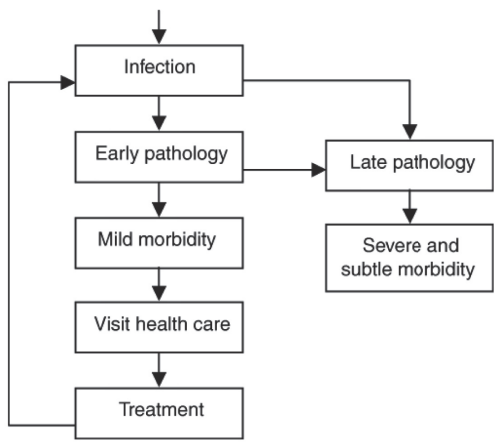

Figure 1.2 Schematic representation of prevention of late schistosomiasis morbidity by early treatment of cases reporting to the health facility with schistosomiasis-related symptoms. Courtesy De Vlas et al. 2004. Trop Med Int Health. 9, A17

In 2001, the Joint Meeting of the Expert Committees on the Control of Schistosomiasis and Soil-transmitted Helminths stressed the need for new research studies that would address current challenges to the control of helminthiasis and recommended investigations into the determinants of effective and efficient health systems-based control by passive case finding or systematic out-patient treatment (WHO 2002). Ghana is currently restructuring its health care delivery system to strengthen the peripheral health facilities. In the decentralized system, integration of control of parasitic diseases including schistosomiasis within the regular health services is central. Health seeking behaviour of people suffering from schistosomiasis-related symptoms is important to determine the potential success of integrated control.

The Ghana health service

Health care delivery in Ghana is based on the Primary Health Care concept adopted in Alma Ata in 1978 to promote essential health care based on practical and socially acceptable methods made universally accessible to individuals and families in the community through their full participation (WHO 1978). The Ghana Health Service is organised in levels of care with the lowest level (Level A) being the Health Post. This is the first point of contact with the formal health service and consists of a Health Assistant who provides basic curative care to patients. Sometime there is also a Traditional Birth Attendant (TBA) who assist in the delivery of babies. The health assistant or the TBA usually does not have formal training and they do not receive formal salary. Cases that cannot be handled at the health post are referred to the health centre, but some times to the distric hospital. The Health Post is not functional in most communities in Ghana at the moment. The next level of care (Level B) is known as the Heath Centre, which is normally staffed with Medical Assistant or a qualified and experienced nurse and supported by auxillary personnel, and mostly without laboratory facilities. In these health care facilities treatment for diseases such as schistosomiasis are usually based on signs and symptoms. The health posts are non-functional in most parts of the country and the health centres now serve as the first point of contact by most patients seeking care from the formal health care delivery. The health centres provide basic curative care for minor cases including schistosomiasis-related symptoms. Usually, first aid is provided to serious cases reporting to the health centres before referring them to the district hospital. The health centres also provide preventive services such as health education to the communities in their catchment areas.

The district hospitals are staffed with one or more qualified medical doctors, nurses and pharmacists. They also have laboratories manned by laboaratory technicians, auxillary nurses and other support personnel. The district hospitals deal with all cases except specialised care, perform surgical operations and refer serious cases to the regional or tertiary hospitals found in the regional capitals. The district hospitals also provide public health services to the towns and villages in their catchment area.

Until recently, the system of payment for health care delivery within the formal sector has been out of pocket payment ('cash and carry') where a patient was required to make full payment for consultation before treatment is provided. Within the cash and carry system, mostly essential drugs are kept in the health facilities. Patients attending these health facilities normally obtain drugs prescribed to them from private pharmacies. The system of payment made it less likely for patients to report to the formal health facilities. Compared to highly debilitating diseases such as malaria

and HIV/AIDS, few people will spend money to seek health care for relatively mild recurring schistosomiasis-related symptoms. The implications are serious though, as severe pathology is a related to severity of the infection. Several studies about the effect of cost recovery policies in Ghana and elsewhere showed that the *cash and carry* system led to a drop in attendance to hospitals, health centres and clinics (Biritwum 1994; Wyss *et al.* 1996) and a concomitant increase in self-medication and other cost savings health practices (Asenso-Okyere *et al.* 1998).

Currently, Ghana is restructuring its health care delivery system to strengthen the peripheral health facilities, sustain integrated, functional and mutually supportive referral care systems, leading to the progressive improvement of comprehensive health care for all, and giving priority to those most in need. In the decentralized health system, integration of control of parasitic diseases including schistosomiasis into the regular health services is central. Also, the Government of Ghana has introduced a new highly subsidised National Health Insurance Scheme in which adult Ghanaians are to pay a monthly minimum subscription of six thousand Ghanaian Cedis (US $0.66). The government caters for treatment of the aged, the poor as well as children of parents who both subscribe to the scheme. The scheme is considered to be the best solution for the health care sector and the only viable alternative to the rigid system of cash and carry which pushed health care far beyond the reach of the ordinary people.

1.5 Health Seeking Behaviour

Theories and models

The complexities of factors that influence the individual's decision making process for obtaining health care complicate health seeking behaviour studies (Jaramillo 1998). Several theories or models have been proposed and used to explain health care seeking behaviour for various diseases (Chrisman 1977; Kroeger 1983; Shaw 1999; Burack *et al.* 2007; Conviser & Pounds 2007; de Almeida *et al.* 2007; Guilfoyle *et al.* 2007; Venmans *et al.* 2007). A theory is a set of interrelated constructs (concepts), definitions, and propositions that presents a systematic view of phenomena by specifying relations among variables, with the purpose of explaining and predicting phenomena whilst model is a hypothetical description of a complex entity or process (Crosby *et al*. 2002; Glanz *et al*. 2002; Kegler *et al*. 2002).

Chrisman (1977) proposed a model that looks into perception and treatment of symptoms by patients, and the interaction of the health care service with patients. Five different stages were proposed namely; (1) *symptom definition* stage which

deals with how patients perceive the physical changes produced by the disease; (2) *illness-related shifts in the role behaviour* referring to the way in which the evolution of symptoms influence how patients relate to their peers; (3) *treatment actions* which examines activities undertaken by patients to alleviate the burden of the illness; (4) the *lay consultation* stage which refers to the exploring of peer's opinion about patient symptoms and suggestions for dealing with them; and (5) *adherence* exploring activities taken by patients following treatment and medical advice.

Kroeger (1983) distinguished two basic models; (1) the *pathway* model and (2) the *determinant* model. The pathway model assumes a logical sequence of steps taken by the individual from manifestation of earliest symptom until use of health care services, whilst the determinant model focuses on assessing variables that can explain the choice of a preferred form of health care service.

The Health Belief Model (HBM) is a psychological model that attempts to explain and predict health behaviours by focusing on attitudes and beliefs of individuals (Rosenstock 1974). The HBM was first developed in the 1950s by social psychologists Hochbaum, Rosenstock and Kegels working in the US Public Health Services (Rosenstock 1974). The model was developed in response to the failure of a free tuberculosis (TB) health screening program. The underlying assumption is based on two factors- (1) the value an individual places on health and (2) the individual's belief that specific preventive actions will achieve the desired goal (see Figure 1.3).

Based on the assumption, the following key variables are identified to form the model: (1) *perceived threat*- entailing perceived susceptibility, risk, severity or seriousness of illness and possible consequences; (2) *perceived benefits*- the effectiveness of strategies to control or alleviate the disease; (3) *perceived barriers*- the physical, psychological and financial factors undermining a negative health action; (4) *cues to action*- events that motivate people to take action; (5) *other demographic, social and structural variables*- that influence health-related behaviour; and (6) *self-efficacy*- the belief in being able to successfully execute the behaviour required to produce the desired outcome.

The Health Belief Model has been applied to a broad range of health behaviours and subject populations (Conner & Norman 1996). It has also been adapted and applied in schistosomiasis health education programmes by integrating socio-economic and cultural factors into the model (Kloos 1995; Schall 1998).

The PRECEDE model was developed by Green and coworkers in the 1950s and has been used to guide various health education and evaluation programmes (Green & Kreuter 1992; Green & Ottoson 1999; Kreuter *et al*. 2003; Green & Kreuter 2005). The model has been applied extensively in lifestyle health education programmes, maternal and child health (Donovan 1991; Burglehaus *et al*. 1997) public health

and disease prevention (Green 1981), assessment of primary care (Bennett 1977), pharmacy interventions (Fedder 1982) and allied health (Goldenhar *et al.* 2001).

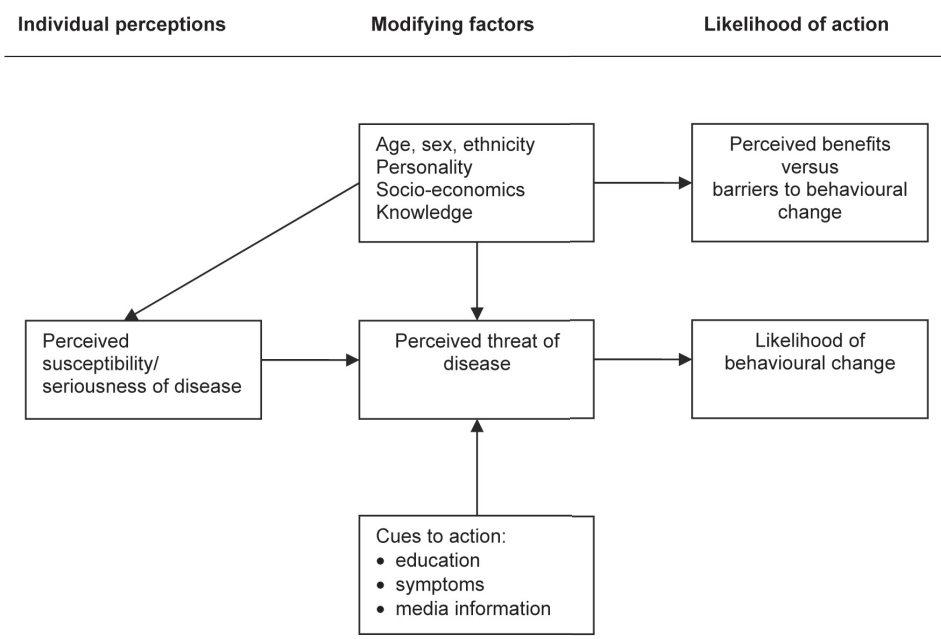

Figure 1.3 Conceptual framework of Health Belief Model. Courtesy Glanz et al. 2002

The primary purpose of PRECEDE model is to organize existing theories and constructs into a cohesive, comprehensive, and systematic view of relations among those variables important to the planning and evaluation of health programs. However, two fundamental propositions are emphasized in the model: (1) health and health risks are caused by multiple factors and (2) because health and health risks are determined by multiple factors, efforts to effect behavioral, environmental, and social change must be multidimensional or multisectoral, and participatory. It can be used as a theoretical or causal model in its applications (Sussman & Sussman 2001) and adaptable to both developed and developing countries setting (Carolina & Gustavo 2003; Hackam & Anand 2003). The model was adapted and used for the control of schistosomiasis in a rural setting in Brazil (Kloos 1995).

The underlying principle of the PRECEDE model is that health education is dependent on voluntary co-operation and participation of the client in a process

which allows personal determination of behavioral practices; and that the degree of change in knowledge and health practice is directly related to the degree of active participation of the client (Green & Kreuter 1991).

Interpersonal models are based on the social learning theory which helps to understand how individuals and environment interact to influence health behaviour. One model called *patient-provider interaction and health care* tries to understand the health professionals' influence on the health behaviour of the patient as well as to develop practices to promote behavioral changes through interactive situations. For example, patients with chronic pain and health care providers are likely to have opposing attitudes and goals, with patients seeking to be understood as individuals and struggling to have their pain concerns legitimized while their health care providers may place a greater focus on diagnosis and treatment than quality of life concerns (Frantsve & Kerns 2007). Basically, this model provides information health care professionals can use to improve the quality of their interactions with patients for successful case management.

In tropical disease control, it has been proposed that the conceptual explanatory models of the *disease*/*health* process and *interventional* actions need to incorporate explanatory dimensions that go beyond biomedical models for morbidity control (Schall 1998; Tanner & Vlassoff 1998). Gazzinelli *et al.* (1998) emphasized the importance of investigating the social and cultural process of the determination of different health risks. Unarguably, health/disease are conceptions constructed in social spaces delimited by the relations established by the production, beliefs, values, access to the formal health services and education, besides other factors.

Design issues of health seeking behaviour studies

Many studies have been conducted over the years in Africa to investigate effects of knowledge, attitude and practices (KAP) on health seeking behaviour for schistosomiasis (Lansdown *et al*. 2002; Wagatsuma *et al*. 2003; Takougang *et al*. 2004; Anguzu *et al*. 2007) and elsewhere in Asia (Sleigh *et al*. 1998; Yu *et al*. 2001) and the Americas (Curtale *et al.* 1998; Gazzinelli *et al*. 1998; Uchoa *et al*. 2000). Health seeking behaviour for other common tropical diseases such as malaria has been investigated extensively across Africa (Falade *et al*. 2006; Beiersmann *et al*. 2007; Deressa *et al*. 2007; Houeto *et al*. 2007), Asia (Sharma *et al*. 2007; Yadav *et al*. 2007) and the Americas (Klein *et al*. 1995; Nieto *et al*. 1999; Rodríguez *et al*. 2003; Vigneron *et al*. 2005). For Sexually Transmitted Diseases (STDs) a large number of KAP and health seeking behaviour studies have been conducted in Africa (Moses *et al*. 1994; Voeten *et al.* 2004) and elsewhere in Asia and the Americas (Garg *et al*. 2007).

Knowledge Attitude and Practices (KAP) and health seeking behaviour studies for schistosomiasis have been obtained mainly from population surveys (Kamunvi & Ferguson 1993; Aryeetey *et al.* 1999; Uchoa *et al*. 2000; Ukwandu & Nmorsi 2004). The design commonly used in KAP studies is cross-sectional employing four main interview techniques; (1) consensus panel (2) focus group (3) natural group and (4) community interview (Isah *et al.* 2007; Ukwandu & Nmorsi 2004; Mfinanga *et al*. 2005; Adeneye *et al*. 2006). Groups of people usually are the unit of analysis whereas for health seeking behaviour studies, the individual or household is the unit of analysis. Some studies combined household surveys with hospital case histories (Harper *et al*. 2003). Designs that target the clinic or hospital for data have commonly been used in Tuberculosis, Sexually Transmitted Diseases and Malaria (Moses *et al*. 1994; Faxelid *et al*. 1998; Parker *et al*. 1999; Fonck *et al*. 2002; Voeten *et al*. 2004).

Regardless of whether the emphasis is on KAP or health seeking behaviour, mostly semi-structured or structured interviews are used to collect data (Coreil 1995). With difficulties in implementing in full any one particular technique of data collection in the field, Jaramillo (1998) suggested that it would be informative for investigators to provide a detailed description of the strategy applied in the interview rather than using generic names such as focus group as these are sometimes misleading.

Determinants of health seeking behaviour

Generally, for a person to decide to seek health care, they must ask whether the symptoms represent a health threat and the resources available to cope with the situation (Shaw 2001).

Various factors influence health seeking behaviour and utilization of the health care facilities. Knowledge about the cause and treatment of the disease (Rousham 1994; Shaw 2001), duration of disease (Jaramillo 1998; Goldman & Heuveline 2000) and perceived severity (Curtale *et al*. 1998) all may influence health seeking behaviour. Hewlett and Cline (1997) observed that severity of symptoms can be an important determinant for passive case reporting to the clinic for urinary schistosomiasis symptoms. Unavailability of drugs (Curtale *et al*. 1998), distance to hospital (Stock 1983) and regime of hospital payment (Biritwum 1994; Wyss *et al.* 1996; Asenso-Okyere *et al.* 1998) have been suggested to influence hospital visit. Also, cultural practices and socio-economic status are thought to influence health seeking behaviour (Adamson *et al*. 2003; Kakai *et al*. 2003; Raso *et al*. 2005).

Guyatt & Evans (1992) pointed out that in control strategies that rely on passive case detection, the community's perception of the disease and socio-economic factors are particularly important in ensuring its effectiveness, since these indicators will affect compliance. We conducted a study across different regions in Ghana to

assess determinants of health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms to contribute evidence needed to guide health planners and policy makers towards integration of schistosomiasis control into the regular health services.

1.6 Schistosomiasis in Ghana

Distribution

The first reported case of schistosomiasis in Ghana dates back to 1895 (MacFie 1920), but the disease assumed a major public health importance in the 1960s after construction of the Akosombo dam (Paperna 1970). The resulting lake Volta, 8,730 km^2 or 3.6% of the country's surface area and a shoreline of 7000 km (Moxon 1984) created a vast area suitable for the breeding of schistosome host snails. In fact, it was described simply as the Man's Greatest Lake (Moxon 1984). Before the construction of the dam, prevalence of *S. haematobium* was between 5-10 % but rose to >90% in most communities along the Volta Lake thus attracting unprecedented international attention (Tokarev 1967a, 1967b; Lavoipierre 1973; Okoh 1980; Scott *et al.* 1982). Other major development projects initiated around the same period of time soon after Ghana's independence in 1957 by constructing a number of clay-core dams in the northern-dry part of the country to enhance village water supplies and agricultural activities contributed to the widespread of schistosomiasis in these areas (Hunter 2003). To date the schistosomiasis situation has been one of the worse in the world (Bosompem *et al.* 2004; Danso-Appiah *et al.* 2004; Shiff *et al.* 2006). Current estimates indicate that over 90% of children living in communities along the Volta Lake are infected, mostly with urinary schistosomiasis (The Partnership for Child Development 1999).

Prior to the 1950s there was no reliable information on distribution of the infection in the country and data were obtained only from hospital records (Furu 1987). Then, from the 1950s the Medical Field Unit was created to be responsible for collecting prevalence information and community-based treatment of infected people but their activity was limited (Onori *et al*. 1963). Large-scale population surveys began in the 1960s following epidemic resulting from creation of the Volta Lake (Okoh 1980). Detailed experiences of the epidemiology and control of urinary schistosomiasis along the Volta Lake in Ghana have been documented elsewhere (Lavoipierre 1973; Chu *et al*. 1978; Chu 1978; Klumpp & Chu 1980; Chu *et al*. 1981; Scott *et al*. 1982). Investigations conducted in other parts of the country showed that urinary schistosomiasis was common in the south with prevalence reaching 75% in some

areas (McCullough 1957). The infection was also recorded in the middle forest region (Vervoorn & Ratulangie 1958; Rosei *et al*. 1966) and the savannah north (Odei 1964).

Control strategies applied in Ghana

Although the rapid spread of the disease along the Volta Basin attracted attention and called for prompt action, initial control measures focused mainly on chemical control targeting the intermediate host snails because effective antischistosomal drugs were not readily available (Sturrock 2001). Chemical control proved to be very expensive, impractical operationally and also raised a number of environmental and health concerns (Chu 1978). The antimonies one of the earliest antischistosomal drugs developed after the First World War were initially tried but discontinued because of serious adverse events (Wolfe *et al*. 1966). In Egypt the antimonies were used to treat only hospital patients because of low compliance associated with the long course of administration, pain from the injections and the serious side effects (Shekhar 1991; Wu & Halim 2000; Cioli *et al.* 1995; Sturrock 2001). Experiences from Egypt showed a high treatment-associated mortality rates estimated at 3 per 1000 patients treated (Jordan 2000; Sturrock 2001). The application of metrifonate began in Ghana in the 1970s but the early 1980s saw large scale implementation across communities along the Volta Lake. However, little success was achieved in terms of controlling prevalence of the infection (Kalitsi 1973; Okoh 1980).

As with other endemic countries, the early 1980s marked the turning point in schistosomiasis control in Ghana when praziquantel was introduced (Cioli *et al.* 1995). The national schistosomiasis control programme was formed around the same time and became active in population-based treatment campaign programmes (Chu 1978, Aryeetey *et al.* 2000). The Partnership for Child Development Programme initiated mass treatment campaign in primary schools along the Volta Basin in the 1990s (The Partnership for Child Development 1999). At the same time an intense schistosomiasis control effort was initiated by Volta River Authority (VRA) in the shoreline communities (VRA Quarterly Report 1996). The VRA Quarterly and Annual Reports (1974-1984) provided general information about the health situation of the villages along the Volta Lake and records of all activities undertaken to alleviate the schistosomiasis problems (Adiamah 1984). Various studies conducted on the health component of the Volta Lake project by World Health Organization (WHO), Akosombo hospital and independent researchers have been analysed and reported (Jones 1973; Odei 1973, 1983). Recently, the experiences of the schistosomiasis control implemented over the years in Ghana were cited by the WHO (WHO 1998).

In spite of the huge internal investment and international assistance for over four decades, urinary schistosomiasis remains widespread in Ghana (Aryeetey *et al.*

2000). The situation was worsened by rapid increase in intestinal schistosomiasis at the lower Volta (Odei 1983; Wen & Chu 1984; Rambajan 1994) and the north (Amankwa *et al.* 1994). Recently, a very intense focus was identified along the Densu Lake (Danso-Appiah *et al*. 2004). Infant schistosomiasis is also becoming a serious public health problem in Ghana (Bosompem *et al*. 2004).

A recent study in Ghana showed 86% cytopathology Papanicolaou-stained smears from people with urinary schistosomiasis had squamous metaplasia (Shiff *et al.* 2006). The data suggest that schistosome-associated bladder cancer may be a big problem in Ghana. Similar documentation has been made in urinary schistosomiasis endemic areas in Ghana (Wagatsuma *et al.* 1999). However, as severe chronic disease is insidious and occurs many years after the infection (Jordan 2000), many deaths may not have been acknowledged to be the result of schistosomiasis. A recent review points out that bladder carcinoma is highest in male adults from Egypt (37.1 per 100,000 person-years) among countries investigated (Murta-Nascimento *et al*. 2007). As the schistosomiasis situation compares Egypt, reduction of early morbidity certainly deserves attention.

1.7 Aim and research questions

The aims of the thesis are to assess antischistosomal drugs, and to explore the possibilities of integrating morbidity control of schistosomiasis within the regular health services. These broad aims will be addressed through studying the following research questions.

1. Is there evidence of resistance against praziquantel for *Schistosoma mansoni* infection?
2. What is the potential of antischistosomal drugs other than praziquantel for treating urinary schistosomiasis?
3. What are the methodological limitations in schistosomiasis control?
4. What are the determinants of health care seeking behaviour for schistosomiasis-related symptoms in Ghana?
5. What are the strengths and weaknesses of integrating morbidity control of schistosomiasis within the regular health services in Ghana?

1.8 Structure of the thesis

The thesis consists of two parts; Part I deals with the first aim and Part II with the second. The research questions 1, 2 and 3 seek to provide answers to Part I on key issues in treatment with antischistosomal drugs, and questions 4 and 5 Part II of the thesis on strengths and weaknesses of integrating schistosomiasis treatment within the regular health service. The research question 1 was addressed by reviewing data on the use of praziquantel in population treatment by standardizing dosage, age, sex, intensity of infection before treatment, sensitivity of diagnosis and time of follow-up after treatment, through a meta-analysis to provide empirical evidence about the possible role of resistance against praziquantel (**Chapter 2**). Question 2 was addressed in **Chapter 3** by a systematic review of evidence from Randomized Control Trials (RCTs). Research question 3 was addressed by a robust assessment of methodological issues relevant to interpretation of research data (**Chapter 4**). Question 4 was addressed in **Chapter 5** and **Chapter 6** by field studies investigating determinants of health care seeking behaviour of patients with schistosomiasis-related symptoms in Ghana. Then, we pooled information from the quantifications resulting from Chapter 5 and a related study on the performance of Ghanaian health care facilities with respect to schistosomiasis to evaluate the potential of integrating schistosomiasis control within the Ghanaian health service (**Chapter 7**). In the General discussion (**Chapter 8**), the five research questions of the thesis are commented on and the implications of the study results for schistosomiasis control discussed. Finally, the implications for policy and research are outlined.

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Chapter 2

Interpreting low praziquantel cure rates of *Schistosoma mansoni* infections in Senegal

Danso-Appiah A, De Vlas SJ. Interpreting low praziquantel cure rates of *Schistosoma mansoni* infections in Senegal. *Trends in Parasitology* 2002;8:125-9.

2.1 Abstract

Praziquantel is currently the drug of choice for the treatment of schistosomiasis. Selective treatment of *Schistosoma mansoni* infections in various endemic countries usually present cure rates of >70% when using the standard dose of 40 mg/kg body weight of praziquantel. However, unusually low cure rates (18-38%) have been reported from Senegal, raising fears for emergence of resistance (or tolerance) to praziquantel. One major problem is the precise quantitative interpretation of cure rates, which allows an unequivocal distinction between drug failure and normal drug performance. This article reviews studies on praziquantel treatment of population by standardizing the data through an innovative meta-analysis and provides empirical evidence concerning the extent to which the reported low cure rates from Senegal are atypical.

2.2 Introduction

Praziquantel (PZQ) is a broad-spectrum schistosomicide introduced in the early 1980s. Currently, treatment of infected individuals or target groups with the standard PZQ dose of 40 mg/kg body weight, the control strategy recommended by WHO, is applied in many endemic countries (WHO 1993). Usually, *Schistosoma mansoni* chemotherapy results in cure rates of >70% and mean egg count reduction rates of >95% 6-12 weeks after treatment (Kumar & Gryseels 1994). Even though re-infection occurs, particularly in children, pathology is resolved or at least the development of pathology is delayed (WHO 19931; Mohamed-Ali *et al*. 1991; Doehring-Schwerdtfeger *et al*. 1992). Currently, no other schistosomicide combines the broad spectrum, easy and safe application at a low price as PZQ (Cioli 1998).

Over the past decade, lower than normal cure rates have been reported from Northern Senegal. Initial studies demonstrated a cure rate of only 18% 12 weeks after selective treatment in the recently established, very intense focus of Ndombo (Gryseels *et al*. 1994; Stelma *et al*. 1995). One explanation for this unusually low cure rate was the emergence of resistance, which alarmed the scientific community (Editorial 1992; Brown 1994). Subsequent trials in the same focus showed cure rates of 31-38% after 6 weeks of follow-up (Gryseels *et al*. 1994; van Lieshout *et al*. 1999) and (perhaps more worryingly) a normal cure rate with 20 mg/kg oxamniquine, the alternative schistosomicide for *S. mansoni* infection (*Stelma et al*. 1997). Subsequent studies in Northern Senegal kept on indicating cure rates lower than usual (Guisse *et al*. 1997; Picquet *et al*. 1998; De Clercq *et al*. 1999; Ernould *et al*. 1999). In mice, *S. mansoni* strains from the Ndombo focus produced isolates less sensitive to PZQ (Fallon *et al*. 1995). It was argued that reduced efficacy of PZQ in the Senegalese isolate was the result of tolerance rather than resistance because the focus had not been subjected to previous drug pressure (Gryseels *et al*. 1994; Fallon *et al*. 1996).

Other explanations were also put forward. The low cure-rates could be expected from the initial intensity of infection in Senegal, where mean egg-loads were extremely high (Cioli 1998; Stelma *et al*. 1995; Picquet *et al*. 1998; Utzinger *et al*. 2000). Even at 95% efficacy, a sufficient number of surviving schistosomes would remain, causing sustained egg excretion in most of the subjects. Moreover, as a result of intense transmission, most individuals might have acquired large numbers of new infections in the weeks before treatment. Immature worms are less sensitive to PZQ (Xiao *et al*. 1985; Sabah *et al*. 1986), therefore many would have escaped drug action and developed into egg-laying adults shortly after treatment (Gryseels *et al*. 1994). Another explanation was based on the fact that PZQ works in synergy with the host immune status (Sabah *et al*. 1985; Brindley & Sher 1987). The Senegalese focus

was a very recent one; hence, an incompletely developed immunity in many subjects could have resulted in the reduced effectiveness of PZQ (Cioli 1998; Gryseels *et al*. 1994).

The treatment outcomes of PZQ field studies from different endemic settings have been pooled together here and the factors that could determine the outcome of population treatment have been quantified by a meta-analysis. The objective is to interpret the low cure rates from Senegal on the basis of trends from other studies to determine the true meaning of such observations.

2.3 Selecting PZQ population studies

All published *S. mansoni* population selective treatment studies with the standard dose of 40 mg/kg of PZQ from a known brand have been collated here. For inclusion of a study, the outcome of treatment had to be expressed as a cure rate (i.e. proportion of treated cases that became negative for *S. mansoni* eggs at follow-up). Only studies with follow-up within 1 month and 1 year were included. Studies with previous PZQ treatment within two years or additional transmission control were excluded. Studies on selected intensities or only morbidity cases (particularly the early clinical trials) were not eligible because they were not representative of usual field situations. To rule out possible bias from age, only studies involving entire communities or representative sub-samples were considered. Inclusion of cases and determination of those cured had to be based on quantitative fecal smears (Katz *et al*. 1972; Teesdale *et al*. 1985). A standard diagnostic test of a single stool specimen was used because cure rates depend on sensitivity (Utzinger *et al*. 2000; De Vlas & Gryseels 1992). Intensity of infection had to be expressed as a geometric mean of number of eggs per gram of faeces (epg) for positive individuals only.

Following a step-wise search of references for published articles, textbooks and MEDLINE, 11 studies (from 1983 to 1999) were suitable for inclusion (Table 2.1). From the studies that compared the effect of different drugs (Stelma *et al*. 1997; Gryseels *et al*. 1987; Polderman *et al*. 1988) or different PZQ dosages (Kardaman *et al*. 1983; Gryseels *et al*. 1987; Polderman *et al*. 1988; Abu-Elyazeed *et al*. 1997), only the results of treatment using 40 mg/kg PZQ were considered. If the results had been presented according to age categories (Stelma *et al*. 1995; Gryseels *et al*. 1987; Polderman *et al*. 1988; Gryseels *et al*. 1991; Abu-Elyazeed *et al*. 1997), they were merged. Similarly, the results from the four cohorts in Ndombo, Senegal (Stelma *et al*. 1995; van Lieshout *et al*. 1999), were also merged. Three studies that presented prevalence before and after treatment could be included because the authors went back to the original data to calculate the cure rates (Ernould *et al*. 1999; Gryseels *et al*. 1991; Barakat *et al*. 1995).

Table 2.1 Studies included in the meta-analysis listed according to year of publication.

Country (year)	N[b]	Follow-up	Diagnosis[c]	Brand of PZQ	Refs
Sudan (1983)	1	4 weeks	1×1×25[d]	Biltricide	Kardaman *et al*. 1983
Burundi (1987)	2	6, 12 weeks	1×2×25	Biltricide	Gryseels *et al*. 1987
Sudan (1988)	1	6 months	1×1×25[d]	Distocide	Homeida *et al*. 1988
Zaire (1988)	1	6 weeks	1×2×25	Biltricide	Polderman *et al*. 1988
Burundi (1991)[a]	2	3, 6, 9, 12 months	1×2×25	Biltricide	Gryseels *et al*. 1991
Egypt (1995)[a]	34	1 year	1×2×42	Distocide	Barakat *et al*. 1995
Egypt (1995)	2	12 weeks	1×1×42	Distocide	El Katsha & Watts 1995
Senegal (1995; 1999)	1	6, 12 weeks	2×2×25[e]	Distocide	Stelma *et al*. 1995; van Lieshout *et al*. 1999
Egypt (1997)	1	8 weeks	3×1×42[f]	Distocide	Abu-Elyazeed *et al*. 1997
Senegal (1999)	1	6 weeks, 4,7 months	1×2×25	Pharmamed	De Clercq *et al*. 1999
Senegal (1999)[a]	2	6, 14 weeks, 7, 10 months	2×2×25[e]	Pharmamed	Ernould *et al*. 1999

[a] Outcomes reported in prevalence. Authors provided cure rates on request.

[b] Number of communities covered by each study.

[c] For diagnosis, e.g. 1×2×25, 1 is the number of stools, 2 the number of Kato-Katz slides per stool and 25 the amount of stool (in mg) per slide.

[d] Teesdale method (Teesdale *et al.* 1985).

[e] Cure rates based on duplicate stool specimens. In the analysis we used cure rates based on a single stool, provided by the authors on request.

[f] Cure rates based on three stool specimens. We used cure rates based on a single stool, as predicted by an egg count model (see text).

Others had to be contacted about the brand of PZQ used. The results from both Senegal studies that used stool specimens on two consecutive days were recalculated from the original data on request by using the first stool only (Stelma *et al*. 1995; Ernould *et al*. 1999). For the study that used three repeated stool specimens (Abu-Elyazeed *et al*. 1997), the result was predicted for one stool using an existing egg count model (De Vlas *et al*. 1992). After standardizing to a single stool specimen, the studies still differed in the number of slides and the amount of stool per slide, ranging from 1 slide with 25 mg to 2 slides with 42 mg of faeces per stool specimen.

Only a limited number of comparable studies are available in the field of schistosomiasis research. There is a lack of uniform methodology and quality data. To obtain, verify and standardize some of the original data has involved substantial effort.

2.4 Meta-analysis

Different communities within a study and repeated follow-ups were each considered as separate data points. A cut-off sample size of >40 persons treated and followed-up was chosen to prevent unrealistic weightings. This led to the exclusion of ten villages (out of 44) from the study by Barakat *et al.* (1995) and two from other studies Ernould *et al.* (1999) and Kardaman *et al.* (1983). Eventually, a total of 63 data points out of 48 communities were available for analysis.

The interdependence between observations (communities and repeated follow-ups) within the same study was accounted for by using generalized linear mixed modeling (GLMM) (Verbeke & Molenberghs 1997) with *study* as a random factor. A logit transformation of cure rates, *ln* [*cure rate* ÷ (100 – *cure rate*)], was used to account for the range of possible outcomes (between 0 and 100%). Subsequently, the best fitting linear combination of co-variates (linear predictor, *Lp*) was obtained from the logit transformed observations. Cure rates (%) can be predicted from Eqn 1:

$$\textit{cure rate} = 100 \div (1 + e^{-Lp}) \qquad [1]$$

The Genstat 5 (REML Variance Component Analysis) was used to estimate the impact, variance and covariance of random and fixed effects. Continuous covariates were centered on their mean values, and significances of the coefficients were assessed by the Wald-test.

Figure 2.1 shows that initial intensity of infection and follow-up time are major determinants of cure rates. Cure rates decrease with intensity of infection for each of the three follow-up categories. Also, short follow-up observations (4-11 weeks) spread on top of points of intermediate follow-up times (3-6 months), which in turn are located above follow-up exceeding 6 months. As depicted by the diverging lines, the decrease of cure rates with intensity is more pronounced in the case of long follow-up (>6 months). This suggests a more important role of re-infection in areas of high intensity of infection.

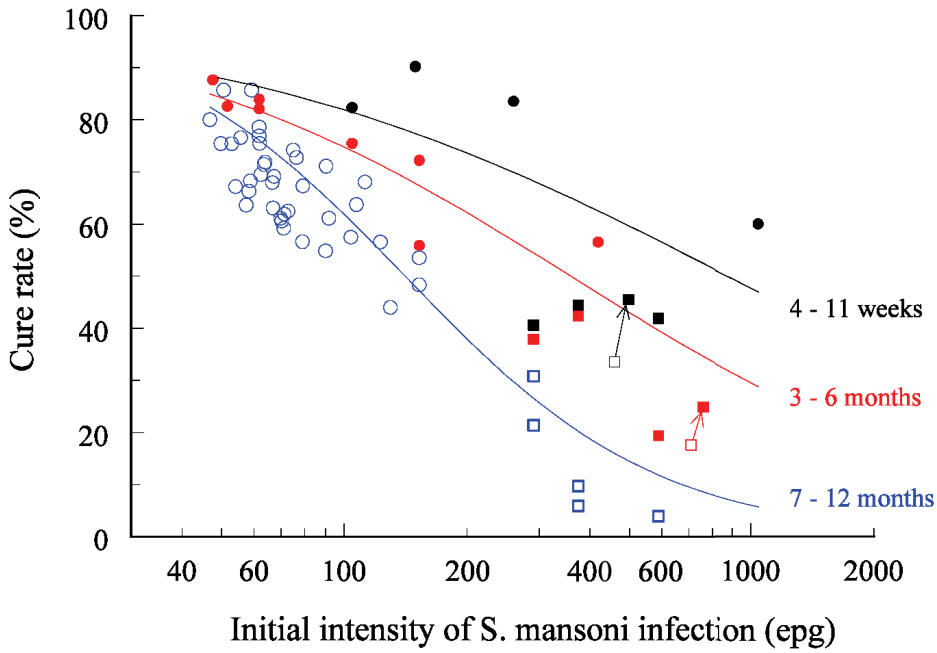

Figure 2.1 The relationship between pre-treatment intensity of Schistosoma mansoni infection and cure rate using the standard praziquantel dose of 40 mg/kg body weight in population-based, selective treatment programmes. Intensity of infection (logarithmic scale) is the geometric mean of egg count per gram of faeces (epg) for individuals positive for S. mansoni eggs. Cure rate denotes percentage of treated subjects who appeared negative for S. mansoni eggs at follow-up. Colours of the dots represent different follow-up time categories: black, 4-11 wk; red, 3-6 mth; blue, 7-12 mth. Data points located on same vertical axis indicate successive follow-ups of a treatment in the same community. Squares, observations from Senegal; circles, studies from elsewhere. Arrows illustrate shifts from published observations from Ndombo (Northern Senegal) based on duplicate stool specimens (open squares) to the corresponding cure rate and intensity from a single stool specimen. For the three follow-up time categories, curves give best fitting associations of cure rate and ln epg through cure rate = $100/(1+e^{-Lp})$, where Lp = a + b ln epg. a and b coefficient values are 4.7 and -0.70 (4-11 wk follow-up); 5.0 and -0.85 (3-6 mth); 6.9 and -1.40 (7-12 mth). Coefficients a and b are estimated by generalized linear mixed modeling (GLMM). Out of the 13 data points from Senegal, 12 are located below the respective lines. Thus, even when initial intensity, follow-up time and sensitivity of diagnosis are accounted for, cure rates from Senegal are consistently lower than expected.

The impact of sensitivity of diagnosis is illustrated by the arrows pointing from the reported (two stools) to the standardized (single stool) cure rates for Ndombo, Senegal. High diagnostic sensitivity leads to detection of more cases with light infections at follow-up and therefore decreases the proportion found negative (Utzinger *et al*. 2000; De Vlas & Gryseels 1992). Also, as more light infections are detected before treatment, the initial intensity of infection decreases. Conversely, less sensitive diagnosis leads to higher initial intensities and higher cure rates at follow-up, therefore the arrows move to the right and upwards. For example, the reported intensity of infection of 708 epg and cure rate of 18% (12 weeks follow-up) in the first Ndombo cohort increased to 759 epg and 25%, respectively, after standardizing to a single stool. Results from another study Ernould *et al.* (1999) showed similar shifts after standardization (data not shown).

Data points from Senegal show high initial egg-counts and are all located on the right-hand side of Figure 2.1. From the general trends, it is not strange that cure rates from Senegal appear rather low. However, the data points are consistently (12 out of 13 data points) lower than those predicted by the model in Figure 2.1. This model employed the linear predictor (Eqn 2) for each of the three follow-up time categories and did not consider Senegal as a factor.

$$Lp = \alpha + \beta \, ln\ epg \qquad [2]$$

In a more detailed analysis, a second model was fitted with *senegal* as a binary covariate, follow-up time as a continuous covariate (in months) and interaction between *ln epg* and *follow-up time*. The resulting linear predictor was (Eqn 3):

$$Lp = 3.16 - (0.28 \times ln\ epg) + (0.28 \times follow\text{-}up\ time) - (0.089 \times ln\ epg \times follow\text{-}up\ time) - (1.45 \times senegal) \qquad [3]$$

All covariates were significant, in particular the binary covariate *senegal* ($P < 0.001$). Other covariates tested (e.g. PZQ brand and sensitivity of diagnosis within one stool specimen) did not show any statistical impact on cure rate and were not included in the model. Out of the other interactions tested, none of them was significant. Also, the random factor *study* was not significant, hence the correction for interdependence between observations within the same study was not necessary. Residual analysis showed a good fit of the complete model to the observations (data not shown).

2.5 Comparing cure rates

Other reports have suggested that the low *S. mansoni* cure rates in Senegal could be explained by the high initial intensities of infection, but they could not quantify this assumption (Cioli 1998; Gryseels *et al*. 1994; Stelma *et al*. 1995; Picquet *et al*. 1998; Utzinger *et al*. 2000). This study provides evidence following standardization and statistical comparison between various population studies that initial, high egg-counts explain part of the deviation of Senegal from average endemic settings. However, even after accounting for intensity of infection and follow-up time, there remained a considerable discrepancy between observations from Senegal and elsewhere. All cure rates from Senegal (Figure 2.1) were lower than those from the three studies with comparable endemicity: Polderman *et al.* (1988) (intensity 1042 epg, cure rate 60%), Homeida *et al.* (1988) (419 epg, 57%) and Kardaman *et al.* (1983) (260 epg, 83%). This discrepancy led to the introduction of the factor *senegal* into the meta-analysis, which indeed proved highly significant.

The magnitudes of the factors contributing to the low cure rates in Senegal can now be obtained from the model equation (Eqn 3). For a normal situation, with initial intensity of infection equal to 100 epg and follow-up time of 3 months, a cure rate of 81% is predicted. In a high endemic situation with 759 epg intensity of infection, such as in the first Ndombo cohort, the cure rate would be 59% (a difference of 22% owing to the effect of intensity of infection). Introducing the factor *senegal* would lead to a further decrease to a cure rate of 25% (a difference of 34% owing to the factor *senegal*). With respect to the originally reported cure rate of 18% based on stool specimens from two consecutive days, the relatively sensitive diagnosis led to another shift of 7%. The relative importance of each of the three factors also applied to the other Senegal observations.

Although high initial intensity of infection and to a lesser extent sensitive diagnosis accounted for part of the downward deviation of cure rates in Senegal from normality, the largest part (represented by the factor *senegal*) remained unexplained. Therefore, based on this study alone, the hypothesis of resistance or tolerance cannot be rejected.

Various biological and methodological aspects concerning the limited likelihood of resistance or tolerance in the Senegal situation have been reviewed (Geerts & Gryseels 2000; Cioli 2000). Other factors such as incompletely developed immunity, very intense re-infection, high numbers of immature worms could also have caused the remaining discrepancy: the findings here might throw more light on these alternatives. First, across the cohorts in Ndombo and successive studies, the discrepancy (i.e. the factor *senegal*) was present and remained within the same order

of magnitude. An incompletely acquired immunity of subjects in this recently exposed community would therefore provide a poor explanation because immune status is expected to have improved over time. Second, the discrepancy did not increase with follow-up time (i.e. statistically, no interaction between the factor *senegal* and follow-up time was found). This means that high rates of re-infection do not provide an explanation. Relatively high numbers of immature worms that are insensitive to PZQ could provide a better explanation. A recent study involving 100 *S. mansoni*-infected schoolchildren from the Richard Toll focus who stayed temporarily in the city of St Louis (non-endemic) also contributed evidence (Gryseels *et al*. 2001). The children (geometric mean egg load of 146 epg) were given a standard dose of 40 mg/kg PZQ three weeks after moving to St Louis with the assumption that the absence of immature worms <3 weeks old would lead to a higher cure rate. Six weeks after treatment, the observed cure rate was 78%. As this value is close to the cure rate of 82% as predicted from the equation above, it suggests a normal performance of PZQ.

2.6 Conclusions

It has been demonstrated here quantitatively that the high pre-treatment levels of infection can partly explain the low cure rates consistently observed in a series of studies in Senegal. The relatively sensitive diagnosis in some of the studies led to a further, limited downward deviation of the observed cure rates. However, even after accounting for intensity of infection and sensitivity of diagnosis, Senegal remained atypical by showing cure rates significantly lower than expected. Although factors relating to the recent nature of this focus (e.g. high numbers of immature worms) could be responsible for the deviating observations from Senegal, the suspicion about tolerance or resistance to PZQ also cannot be ruled out. The results from this meta-analysis can help field researchers to decide to what extent future low cure rates deviate from expected.

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Chapter 3

Drugs for treating urinary schistosomiasis

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3.1 Abstract

Urinary schistosomiasis causes long-term ill-health. This review examines the various treatment options and newer drugs. To evaluate antischistosomal drugs, used alone or in combination, for treating urinary schistosomiasis. In August 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, LILACS, *m*RCT, and reference lists of articles. We also contacted experts in schistosomiasis research. Randomized and quasi-randomized controlled trials of praziquantel, metrifonate, artemisinin derivatives, or albendazole, alone or in combination, versus placebo, different doses, or other antischistosomal drugs for treating urinary schistosomiasis. One author extracted data, and assessed eligibility and methodological quality, which were cross-checked by a second person. Dichotomous outcomes were combined using risk ratio (RR), and continuous data were combined using weighted mean difference (WMD); both presented with 95% confidence intervals (CI). Twenty-four trials (6315 participants) met the inclusion criteria. Compared with placebo, participants receiving metrifonate had fewer parasitological failures at follow up at one to three months (1 trial) and three to 12 months (3 trials). Egg reduction rate was over 90%, and no adverse events were reported (1 trial). One metrifonate dose was inferior to three doses given fortnightly (both used 10 mg/kg). Praziquantel (standard single 40 mg/kg oral dose) was more effective than placebo at reducing parasitological failure at one to three months' follow up and three to 12 months. Egg reduction rates were improved with praziquantel (over 95% versus 5.3% to 64% with placebo). Mild to moderate adverse events were recorded in two trials. A comparison of metrifonate (10 mg/kg x 3, once every 4 months for one year) with praziquantel (standard dose) showed little difference in parasitological failure. For praziquantel, there was no significant difference in effect between 20 mg/kg x 2, 30 mg/kg x 1, and 20 mg/kg x 1, and the standard dose for all outcomes. One small trial of artesunate showed no obvious benefit compared with placebo, and the artesunate-praziquantel combination was similar to praziquantel alone. Praziquantel and metrifonate are effective treatments for urinary schistosomiasis and have few adverse events. Metrifonate requires multiple administrations and is therefore operationally less convenient in community-based control programmes. Evidence on the artemisinin derivatives is currently inconclusive, and further research is warranted on combination therapies. We suggest metrifonate be reconsidered for the WHO Model List of Essential Medicines.

3.2 Plain language summary

Worms residing in blood vessels of the bladder cause a chronic disease known as urinary schistosomiasis. The disease is commonly found in African and Eastern Mediterranean countries, especially in poor, rural areas. Humans become infected when they come into contact with contaminated water. The infection occurs when small larvae shed from snails in infected waters get into the individual through the skin and develop into adult worms that travel to the blood vessels of the bladder. There they can produce a large number of eggs, and the worm can live for three to five years. It is mainly the eggs that cause the disease. The main symptoms are blood in the urine and pain when passing urine. The eggs also cause tissue damage, and the severity of disease depends upon the intensity of the infection. Sometimes the infection can lead to bladder cancer or other kidney problems, including kidney failure. There are a number of measures that have been introduced to try to reduce the risk of infection. These include health education, improving clean water supplies and sanitation, environmental control measures to reduce numbers of intermediate host snails, and drug treatments. The review looked at the efficacy of drugs to reduce the ill-health associated with these infections. The review identified 24 trials involving 6315 people. Praziquantel and metrifonate were both found to be efficacious with few adverse events, although adverse outcomes were poorly assessed. Evidence on the artemisinins was inconclusive, and further research is warranted on combination therapies.

3.3 Background

Urinary schistosomiasis is caused by the blood fluke, *Schistosoma haematobium*. The disease, which causes chronic ill-health, is endemic in most African and Eastern Mediterranean countries (Chitsulo *et al*. 2000; Engels *et al*. 2002; Steinmann *et al*. 2006). It is especially important in poor, rural areas where attempts to alleviate poverty also promote water resources development that may increase transmission and hence exacerbate the disease burden (Danso-Appiah *et al*. 2004; Fenwick 2006; Steinmann *et al*. 2006). In some areas of sub-Saharan Africa there is an overlap in distribution with *S. mansoni* resulting in mixed infections (WHO 2002). The two parasites infect about 131 million people (Davis 2003) and are associated with considerable morbidity and even mortality (van der Werf *et al*. 2003). A recent meta-analysis suggested that the burden due to schistosomiasis has been significantly underestimated, since disability weights might be two to 15 times higher

than previously estimated (King *et al*. 2005). The social and economic burden of schistosomiasis is thought to be even greater (WHO 2002).

Mode of infection

The infection is acquired through contact with freshwater infested with the infective cercariae shed from the intermediate host snail (*Bulinus* spp.). Once cercariae have penetrated the human skin, the parasites develop into the adult worm within, on average, 63 to 65 days (Smith *et al*. 1976; Ghandour 1978), and the worms usually migrate to the blood vessels draining the bladder where they reside and produce large numbers of eggs. On average, adult worm pairs live for three to five years, but some can live up to 30 years with the reproduction potential of one schistosome pair estimated to be up to 600 billion schistosomes (Gryseels *et al*. 2006). The eggs of *S. haematobium* have a terminal spine and must traverse the bladder tissues towards the lumen of the bladder and urinary tract for elimination via urine. In the process, a considerable number become trapped in the bladder walls and surrounding tissues to initiate immune-induced inflammatory reactions, which subsequently lead to morbidity. It is important to note that eggs trapped in the tissues cause disease rather than the worms themselves.

Symptoms and effects

The disease can present as chronic, which is most common, or acute. Haematuria (blood in urine) and dysuria (painful urination) are the main early symptoms of the disease. For most people who are regularly exposed, the severity of disease depends upon the intensity of infection. Mostly individuals with few schistosome worms, and especially adults, remain asymptomatic, although about 80% of infected children show early symptoms and signs of disease (Mott *et al*. 1983; Olds & Srinivasan 2000). Late-stage complications are insidious and include calcification of the bladder wall, bladder stones, and secondary bacterial infection (Jordan *et al*. 1993). Tissue damage caused by trapped eggs can lead to diffuse or localized wall thickening of the bladder and the distal ureter hydronephrosis or hydroureter, which may eventually lead to kidney failure (Kardorff & Doehring 2001; WHO 2002; van der Werf *et al*. 2003).

Elevated urine albumin levels and reported pain upon micturition by children have a strong correlation with *S. haematobium* infection (Rollinson *et al*. 2005). An important long-term consequence of infection is squamous cell carcinoma of the bladder (Jordan *et al*. 1993; King *et al*. 2005; Shiff *et al*. 2006). A recent review points out that bladder carcinoma is the seventh most common cancer worldwide in men and that the highest incidence rate among men is found in Egypt (37.1 per

100,000 person-years) (Murta-Nascimento *et al*. 2007), which might be related to *S. haematobium* infection and morbidity (Jordan 2000). Eggs produced in venous blood vessels elsewhere such as the vertebral column, and resulting in granuloma formation, may cause spinal cord compression and neurological complications. Severe chronic disease occurs later in life following the infection, and many deaths are rarely acknowledged to be due to schistosomiasis because there is hardly any recognition of the link between infection in early life and later development of severe disease.

Sustained heavy infection leads to iron deficiency anaemia and other nutritional deficiencies, especially in children (Awasthi *et al.* 2003; King *et al*. 2005). The disease often results in retarded growth, reduced physical activity, and impaired cognitive function in children (Stephenson 1993; Nokes *et al.* 1999; PCD 1999; Jukes *et al.* 2002; WHO 2002).

Diagnosis

Parasitological diagnosis by microscopy of urine for parasite eggs is the most practical and widely used method for identifying infected individuals (Hassan *et al*. 1994). Egg output in urinary schistosomiasis can be influenced by several factors, such as time of collection of urine (peak egg excretion occurs around noon), day-to-day variations, seasonal variations, and environmental conditions (Braun-Munzinger & Southgate 1992). Therefore negative results following microscopic examination of a single urine specimen, as with a single stool for intestinal schistosomiasis, are not reliable, particularly in areas characterized by low intensities of infection (de Vlas *et al*.1992). Indeed, measurement of prevalence and intensities of infection by egg count has shortcomings (Gryseels & De Vlas 1996; de Vlas *et al*. 1997; Utzinger *et al*. 2001b). Egg count is quantified using a nucleopore membrane by urine filtration of a standard 10 mL volume of urine. Reagent strips for detecting blood in the urine (haematuria), and recently, monoclonal antibody-based dipstick tests for detecting schistosome-specific by-products are used to diagnose the disease (Bosompem *et al*. 1997; Bosompem *et al*. 2004). Clinically, the disease is diagnosed by reported terminal blood after urination or by inspecting urine for haematuria. Diagnosis on the basis of presence of blood in urine is less reliable in adults (RUSG 1995; Ansell *et al*. 1997). This is because blood in the urine of an adult may be due to causes other than urinary schistosomiasis. Ultrasound was introduced in the 1970s to detect schistosomal pathology first in the hospital and then in field studies (Hatz 2001). It is a safe, rapid, non-invasive, and relatively inexpensive technique for assessing bladder or urinary tract pathology both in the hospital and in community surveys (Hatz *et al*. 1990).

Disease control strategies

There is no effective antischistosomal vaccine (Gryseels 2000; Fenwick *et al*. 2006), although significant progress has been made in recent years (McManus & Loukas 2008). Therefore, schistosomiasis control programmes have the primary objective of reducing the burden of disease. Four main control strategies have been employed with varying success.

– **Health education** to promote good hygiene and sanitation, especially among school-aged children and caregivers. It discourages practices such as bathing in streams and indiscriminate disposal of refuse that tend to increase risk of the infection. The ultimate goal is to decrease the number of eggs reaching and contaminating the environment, particularly freshwater bodies. However, the long-term impact of health education on the transmission of schistosomiasis in rural traditional communities is questionable (Kloos 1995; Sow *et al*. 2003).
– **Water supply and sanitation** to reduce frequency of water contact for most domestic activities such as fetching water for drinking, washing clothing, or bathing in streams and ponds; and access to adequate sanitation to avoid environmental contamination with parasite eggs.
– **Control of the intermediate host snail** by environmental management such as removal of vegetation around banks of streams and lining irrigation canals with concrete slabs (Steinmann *et al*. 2006); and treating infested water bodies with molluscicide to destroy the intermediate host snail. The important role environmental management as part of an integrated control approach has played in conquering *S. japonicum* in China has been emphasized (Utzinger *et al*. 2005).
– **Morbidity control** by chemotherapy of the human population aims to reduce disease burden and thereby transmission. Past control measures focused largely on reducing or interrupting transmission, but such measures have not been sustainable due to high cost and operational difficulties (WHO 2002). The advent of safe, efficacious, and inexpensive drugs shifted the emphasis to morbidity control in areas of high disease burden, endorsed by the World Health Organization (WHO) in the mid-1980s (WHO 1993; WHO 2002), while in low-burden areas the emphasis is to interrupt transmission of the infection. Although chemotherapy has emerged as the most cost-effective control strategy because of availability of inexpensive drugs, it has been suggested that in most endemic areas addition of preventive measures focusing on clean water, adequate sanitation, and health education to complement chemotherapy is necessary to achieve long-term sustainable schistosomiasis control (Utzinger *et al*. 2001a; Singer & de Castro 2007).

Chemotherapy

Chemotherapy is targeted especially at school-aged children (Magnussen *et al*. 2001; WHO 2002; Savioli *et al*. 2004). The assumption is that reducing the worm burden in childhood, when infection intensity is highest, will prevent most long-term complications occurring later in adulthood.

Several drugs have been used or tried for the treatment of urinary schistosomiasis and later abandoned because of poor effect or adverse events: antimonials, niridazole, lucanthone, hycanthone, oltipraz, cyclosporin A, levamisole, and oxamniquine; see Cioli *et al*. (1995) for a comprehensive review.

Current treatment options are limited to praziquantel and metrifonate.

– **Praziquantel** is the only drug on the WHO Model List of Essential Medicines for treating *S. haematobium*. This broad-spectrum antischistosomal drug is effective against all *Schistosoma* species, although it is refractory against immature parasites (Sabah *et al*. 1986). Praziquantel is administered orally at a standard dose of 40 mg/kg body weight. The most common adverse effects are gastrointestinal, including abdominal pain, nausea, vomiting and diarrhoea, and are usually mild and last less than 24 hours.

– **Metrifonate** was introduced as a drug for humans in the 1960s (Snellen 1981) and has been used extensively to treat urinary schistosomiasis. The standard dose of 7.5 to 10 mg/kg given three times at 14-day intervals has been used extensively and is mostly well tolerated (Forsyth & Rashid 1967; Davis & Bailey 1969; Rugemalila & Eyakuze 1981; Feldmeier & Doehring 1987). Adverse effects are mainly as a result of cholinergic stimulation and include fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhoea, nausea, vomiting, and bronchospasm. Its use has been limited after a suggestion that it was inferior clinically, economically, and operationally to praziquantel (Feldmeier & Chitsulo 1999). Subsequently, metrifonate was withdrawn from the WHO Model List of Essential Medicines (Cioli 2000; Utzinger & Keiser 2004).

Other drugs have potential as treatment options for urinary schistosomiasis, such as artemisinin derivatives, albendazole, and amoscanate. Albendazole is often administered together with praziquantel for simultaneous control of schistosomiasis and soil-transmitted helminthiasis.

– **Artemisinins.** The antischistosomal activity of the artemisinins, such as artesunate and artemether, was discovered in the early 1980s (Le *et al*. 1982; Le *et al*. 1983). The artemisinins are active against the liver stages (immature) worms,

while the invasive stages and adult worms are less susceptible to the drugs. Adverse effects are minor and last for less than 24 hours. Artemisinin monotherapy may not be beneficial due to stage-specific activity, but combination with existing drugs effective against other stages (eg praziquantel) may improve therapeutic efficacy.

– **Albendazole** is indicated for the treatment of a variety of worm infestations. In recent years it has often been co-administered with praziquantel with the goal of simultaneously controlling schistosomiasis and soil-transmitted helminthiasis (Friis *et al*. 2003; Zhang *et al*. 2007). Albendazole is administered orally (usually as single 400 mg dose), and reported adverse effects include gastrointestinal upsets, headaches, and dizziness, while rash, fever, elevated liver enzymes, and hair loss occur less frequently. There have been reports of elevated liver enzymes, headaches, loss of hair, low levels of white blood cells (neutropenia), fever, and itching if taken at higher doses and/or for a long period of time.

– **Amoscanate** is a broad-spectrum anthelminthic drug that exhibits activity against all major human schistosome parasites (Striebel 1976), other systemic parasites (eg filariae), and gastrointestinal nematodes (eg hookworms). It has been tested extensively in China using the locally produced equivalent called 'nithiocyaminum' (Bueding *et al*. 1976; Striebel 1976). Toxicity in experimental animals was quite low, and mutagenicity tests in bacteria gave negative results; however, mutagenic metabolites were detected in urine of mammals given amoscanate (Batzinger & Bueding 1977). It was abandoned because of concerns over liver toxicity and availability of better drugs, such as praziquantel (Cioli *et al*. 1995). It is possible that amoscanate may represent a unique, broad-spectrum schistosomicide with the appropriate structural modifications to decrease liver toxicity (Cioli *et al*. 1995).

Combinations of antischistosomal drugs have also been tested with the aim of improving therapeutic efficacy.

– **Artemisinin derivatives (artesunate or artemether) plus praziquantel.** This combination is suggested because artesunate and artemether are effective against immature worms, and artemether has shown in mouse models to prevent infection. Combining artesunate or artemether with praziquantel, which is effective against adult worms, may improve therapeutic efficacy.

– **Metrifonate plus praziquantel.** The rationale for this combination is that both drugs are independently effective against *S. haematobium* and that their targets of action in the parasite are not linked. Combination may improve therapeutic efficacy by offering mutual protection to each drug, and it may also slow or prevent the development of resistance.

– **Albendazole plus praziquantel.** Albendazole has broad activity, and it has been suggested that combining with praziquantel may help improve therapeutic efficacy. This combination has not been tested widely.

Praziquantel is virtually the only drug currently available for clinical management and control of urinary schistosomiasis. The sharp reduction in price of praziquantel has stalled advancement of other potential control options, such as vaccines, new drugs, and diagnostics (Utzinger *et al*. 2007). It is noteworthy that pressure on praziquantel is growing, following the policy adopted at the 54th World Health Assembly to increase distribution of the drug and treat at least 75% of school-aged children and other high-risk groups living in areas with high burden of the disease by 2010 (Colley *et al*. 2001; WHO 2002; Hagan *et al*. 2004), and new efforts made by the Schistosomiasis Control Initiative to treat millions of school-aged children in selected African countries (Fenwick *et al*. 2006). It is therefore timely to assess other antischistosomal compounds as potential alternatives should resistance to praziquantel develop, compare metrifonate with praziquantel as a potentially useful second-line drug, and assess the potential of combination treatments.

3.4 Objectives

To evaluate antischistosomal drugs, used alone or in combination, for treating urinary schistosomiasis. Specifically:

– Praziquantel, metrifonate, and artemisinin derivatives versus placebo; and to assess the appropriate dose for each from randomized comparisons by dose.
– Praziquantel versus metrifonate.
– Praziquantel plus other drugs (eg metrifonate, albendazole, or artemisinins) versus praziquantel alone.

Other relevant drugs or comparisons will be included in the future if they help address relevant safety, efficacy, or policy questions.

3.5 Methods

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Individuals infected with *S. haematobium* diagnosed either microscopically for the presence of *S. haematobium* eggs in a standard filtrate of 10 mL of urine or by haematuria in endemic areas.

Types of interventions

Praziquantel, metrifonate, artemisinin derivatives, or albendazole alone or in combination versus placebo or different doses of same drug; or other relevant antischistosomal drugs.

Types of outcome measures

Primary

Parasitological failure, defined as treated individuals who remained positive for eggs in the urine at follow up (distinguishing between one to three and three to 12 months post-treatment). Egg reduction rate (one to three or three to 12 months post-treatment).

Secondary

Laboratory indices

- Reduction in the percentage of people with a heavy infection (currently defined as ≥ 50 eggs/10 mL urine (WHO 2002).
- Clearance of haematuria.
- Measures of anaemia (mean haemoglobin; proportion of participants anaemic).

Functional indices *(measured by standardized replicable techniques)*

Resolution of bladder or urinary tract pathology, as measured by ultrasound, by standard international classification (CWG 1992; Richter *et al*. 1996), or other standardized methods. Physical growth, including weight-for-age, height-for-age, weight-for-height, upper mid-arm circumference, and triceps skinfold thickness. Physical fitness. Cognitive function and educational achievement.

Adverse events

- Serious (fatal, life-threatening, requiring hospitalization, or discontinuation of treatment).
- Other.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Databases

We searched the following databases using the search terms and strategy described in Table 3.1: Cochrane Infectious Diseases Group Specialized Register (August 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 3); MEDLINE (1966 to August 2007); EMBASE (1974 to August 2007); and LILACS (1982 to August 2007). We also searched the *meta*Register of Controlled Trials (*m*RCT) using '*Schistosoma haematobium*' as the search term (August 2007).

Researchers and organizations

We contacted individual researchers working in the field and experts from the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) for unpublished data and information on ongoing trials.

Table 3.1 Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	Schistosoma haematobium	SCHISTOSOMIASIS HAEMATOBIA	SCHISTOSOMA HAEMATOBIA	SCHISTOSOMA-HAEMATOBIA	Schistosoma haematobium
2	praziquantel	urinary schistosomiasis	urinary schistosomiasis	urinary schistosomiasis	urinary schistosomiasis
3	metrifonate	1 OR 2	1 OR 2	1 OR 2	1 or 2
4	albendazole	praziquantel	praziquantel	praziquantel	praziquantel
5	artesunate	metrifonate	metrifonate	metrifonate	metrifonate
6	artemether	albendazole	albendazole	albendazole	albendazole
7	2-6/OR	artesunate	artesunate	artesunate	artesunate
8	1 AND 7	artemether	artemether	artemether	artemether
9	—	4-8/OR	4-8/OR	4-8/OR	4-8/OR
10	—	3 AND 9	3 AND 9	3 AND 9	3 AND 9
11	—	—	Limit 10 to human	Limit 10 to human	—

[a]Cochrane Infectious Diseases Group Specialized Register.

[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins & Green 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

Reference lists

We checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Anthony Danso-Appiah (ADA), with assistance from Vittoria Lutje, the Cochrane Infectious Diseases Group (CIDG) Information Retrieval Specialist, searched the literature and retrieved studies. ADA screened the results to identify potentially relevant trials and assessed the eligibility of trials for inclusion in the review using an eligibility form based on the inclusion criteria; Paul Garner (PG) verified these procedures. ADA scrutinized each trial to ensure it has been included only once. If different parts of the same data were reported in different publications, ADA identified them and linked the data to the parent study. ADA attempted to contact the authors of potentially relevant trials for clarification if eligibility was unclear and listed all potential studies excluded along with the reason for exclusion in the Characteristics of excluded studies.

Data extraction and management

ADA extracted data of trial characteristics such as methods, participants, interventions, and outcomes. ADA recorded the data on standard forms, which PG cross-checked. ADA and PG resolved discrepancies through discussion and contacted Jianping Liu (JPL), Piero Olliaro (PO), and Jürg Utzinger (JU) on technical issues. Data were double-entered and cross-checked to make sure there were no errors. ADA scrutinized each trial to identify multiple publications from a single data set and attempted to contact trial authors for clarification, or insufficient or missing data. ADA extracted the number of participants randomized and number analysed in each treatment group, which allowed us assess the most appropriate type of analysis to carry out and to calculate the percentage loss to follow up. For dichotomous outcomes, ADA recorded the number of participants experiencing the event in each group of the trial. For continuous outcomes summarized using geometric mean, ADA extracted means and their standard deviations on the log scale when provided. If the data were provided as arithmetic mean, ADA extracted the means for each group and their standard deviations (SD), standard error (SE), or confidence interval (CI), where possible.

Stratified data were extracted according to the stratifications and follow-up times. Most included trials defined intensity of infection by egg count as light, moderate, and heavy (instead of according to WHO 2002), and we based the treatment failure rate on these categories. We extracted information such as brand of drug used,

dose, participant age, diagnostic criteria, endemicity, whether the trial was hospital- or community-based, and whether there had been simultaneous application of other control measures during the trial (eg health education or use of molluscides). To allow assessment of the interdependence between observations in a trial, we extracted data on repeated follow ups and number of communities involved in each trial. Data on haematuria from King *et al*. 2002 were extracted from graphs.

Assessment of risk of bias in included studies

ADA examined design issues relating to internal validity, and PG checked the assessment. Generation of allocation sequence was described as adequate if the method used indicated that the resulting sequences were unpredictable, unclear if trial was randomized but method not described, inadequate if sequences could be predicted, or not described (Jüni *et al*. 2001). Allocation concealment was described as adequate if methods used prevented prior knowledge of investigators enrolling participants and participants of treatment assignment, inadequate if participants and investigators enrolling participants could foresee upcoming assignment, or not described (Jüni *et al*. 2001). ADA noted who was blinded to the interventions, such as the participants, care providers, or outcome assessors. The inclusion of all randomized participants in the main analysis was assessed as adequate if more than 90% were included in the analysis, inadequate if 90% or less, or unclear. Given that these cut-offs are arbitrary and subject to sample size for a given study, ADA also reported actual percentages. ADA reported the overall number randomized and the number included in the review for trials not using all the trial arms in the analysis.

Data synthesis

Review Manager 4.2 was used for the statistical analyses and dichotomous outcomes (failure rates) were presented as risk ratios (RR) with 95% confidence intervals (CI). To minimize selection bias and the effect of participant attrition, we calculated the proportion of parasitological failure from the total number of participants at follow up and conducted per protocol analysis. We considered RR to be more appropriate because event rates were high. We intended to analyse by intention-to-treat, but this was not possible due to the lack of information in some trial reports. Continuous data were presented as weighted mean differences (WMD) with their standard deviation (SD) or standard error (SE). Egg counts were reported mostly as percentage reduction in geometric mean with rates of reduction over 90% across trials irrespective of background drug or dose. Because treatment effects were obvious in terms of egg excretion, we decided to report them in a table instead of combining in a meta-analysis.

The effects were obvious in comparisons against placebo; therefore we restricted the analysis to the two primary outcomes, three secondary outcomes, and adverse events. We expressed them by number-needed-to-treat (NNT), where possible, and related this to background endemicity.

The impact of follow-up time on cure rate has been elucidated and interpreted from the analysis of available research data; short follow-up times give better treatment effect in terms of parasitological cure than long follow-up times of same background drug and endemicity (Danso-Appiah & De Vlas 2002). To account for this, we analysed treatment failure based on two follow-up categories as short (one to three months) and long (three to 12 months), and also according to dose.

Where data were sufficient we conducted sensitivity analyses to assess the robustness of the results to the quality components. We tested for heterogeneity using the chi-squared and I^2 tests, and overall effect with Z score at 95% CI. We attempted to explore potential publication bias using funnel plots, but this was not possible because of the limited number of trials in comparisons.

3.6 Results

Description of studies

See: Characteristics of included studies (Appendix); Characteristics of excluded studies (Appendix).

Twenty-four trials (6315 participants), reported in 35 published articles, met the inclusion criteria (see Characteristics of included studies; Appendix); none were cluster-randomized. Four articles were published from the same trial data (King *et al*. 1988), and another three from the same study (Stephenson *et al*. 1989). Wilkins & Moore 1987 reported two trials, but we included one (Nyamari trial named Wilkins & Moore 1987) and excluded the other (Simote trial named Wilkins & Moore 1987b) because the latter did not randomize the participants. Nineteen trials were excluded from the review (see Characteristics of excluded studies; Appendix).

Of the 24 trials included in the analysis, 20 evaluated praziquantel (eight specified Biltricide (Bayer)). Nine trials assessed metrifonate (three specified Bilarcil (Bayer)). Three trials assessed the combination of praziquantel with albendazole, and one trial assessed praziquantel plus artesunate. For the two primary outcomes, 21 trials reported cure rate or failure rate, and 20 reported egg reduction rate. Nine trials reported adverse events. There was lack of uniformity in diagnostic criteria (Table 3.2) and classification of intensity of infection across trials (Table 3.3). The WHO classifies the intensity of infection as light (1 to 49 eggs/10 mL urine) or heavy (≥

50 eggs/10 mL urine) (WHO 2002). However, the trials used different classifications for light infection (eg 1 to 5, 1 to 29, 60 to 249, and 250 to 500 eggs/10 mL urine). Moderate and heavy infections were classified the same way with often considerable overlaps between intensity categories.

Table 3.2 Diagnostic criteria pre- and post-treatment

Trial	Pre and post differ?	Diagnostic criteria
Aden Abdi & Gustafsson 1989	No	10 mL of single urine
Beasley *et al*. 1999	No	10 mL of single urine
Befidi-Mengue *et al*. 1992	No	10 mL of single urine
Jewsbury & Cooke 1977	Yes	10 mL of single urine vs 10 mL of 3 daily urines
Pugh & Teesdale 1983	No	10 mL of single urine
Omer 1981	No	10 mL of single urine
Rey *et al*. 1983	No	10 mL of single urine
Rey *et al*. 1984	No	10 mL of single urine
Stephenson *et al*. 1985	No	10 mL of urine adjusted for whole volume
Stephenson *et al*. 1989	No	10 mL of urine adjusted for whole volume
Borrmann *et al*. 2001	No	10 mL of 2 daily urines
Kardaman *et al*. 1985	No	10 mL of 2 daily urines
King *et al*. 1988	No	10 mL of 2 daily urines
King *et al*. 1989	No	10 mL of 2 daily urines
King *et al*. 2002	No	10 mL of 2 daily urines
Olds *et al*. 1999	Yes	10 mL of 2 daily urines vs 10 mL of single urine
Davis *et al*. 1981	No	10 mL of 3 daily urines
Doehring *et al*. 1985	No	10 mL of 3 daily urines
McMahon & Kolstrup 1979	No	10 mL of 3 daily urines
McMahon 1983	No	10 mL of 3 daily urines
Oyediran *et al*. 1981	No	10 mL of 3 daily urines
Taylor *et al*. 1988	No	10 mL of 3 daily urines
Wilkins & Moore1987a	No	10 mL of 3 daily urines
Jinabhai *et al*. 2001	Not stated	Not stated

Trial setting and participants

The trials were conducted in Africa: nine in East Africa (six in Kenya and three in Tanzania); five in Southern Africa; four in the Horn of Africa (three in Sudan and one in Somalia); four in West Africa; and two in Central Africa. Nineteen trials were conducted in the 1980s, shortly after praziquantel was introduced in the market, one in the early 1990s, and three in the new millennium. Twenty-two trials involved children aged up to 15 years; the other two trials recruited only boys (Doehring *et al*. 1985; Befidi-Mengue *et al.* 1992). Four trials recruited children with mixed infection of *S. haematobium* and *S. mansoni* (Jewsbury *et al*. 1977; Doehring *et al*. 1985; Kardaman *et al*. 1985; Taylor *et al*. 1988). Participants were identified in community surveys in all except two trials that recruited patients attending hospital (Davis *et al*. 1981) or a combination of patients attending hospital and participants detected during a field survey (Omer 1981).

Table 3.3 Intensity of infection categories: classifications used by trials

Trial	Light	Moderate	Heavy
King *et al*. 1988	1 to 99	100 to 399	400+
King *et al*. 1989	1 to 99	100 to 399	400+
King *et al*. 2002	1 to 99	100 to 399	400+
McMahon 1983	250 to 500	501 to 1000	1000+
Omer 1981	60 to 249	250 to 499	500+
Rey *et al*. 1984	1 to 5	6 to 50	51+
Stephenson *et al*. 1985	1 to 29	30 to 99	100 to 500
Stephenson *et al*. 1989	1 to 29	30 to 99	100 to 499
Taylor *et al*. 1988	< 100	—	100+

Risk of bias in included studies

See the Characteristics of included studies (Appendix) and summary of the risk of bias (Table 3.4).

The methods used to generate the allocation sequence were adequate in the 11 trials that used computer-generated numbers, random-number tables, randomized cards, permutation table, or randomized block design. One trial used sequential allocation (inadequate; Pugh & Teesdale 1983), and the methods used to generate the allocation sequence were unclear in 12 trials. Only three trials used adequate methods to conceal allocation (Aden Abdi & Gustafsson 1989; Olds *et al*. 1999; Borrmann *et al.* 2001); the methods were unclear in the remaining 21 trials. Eight trials employed blinding and described who was blinded (six were double-blind and

two single-blind); the remaining were unclear. For follow up at one to three months, 17 trials included 90% or more participants in the analysis (adequate), and two trials were unclear. For follow up at three to 12 months, 12 trials included 90% or more participants in the analysis (adequate) and five trials were unclear.

Table 3.4 Risk of bias of included trials

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of randomized participants in analysis
Aden Abdi & Gustafsson 1989	Adequate	Adequate	Assessors	Inadequate
Beasley *et al*. 1999	Adequate	Unclear	Assessors	Inadequate
Befidi-Mengue *et al*. 1992	Unclear	Unclear	Unclear	Unclear
Borrmann *et al*. 2001	Adequate	Adequate	Participants and investigators	Adequate
Davis *et al*. 1981	Adequate	Adequate	Participants, investigators, and assessors	Adequate
Doehring *et al*. 1985	Unclear	Unclear	Unclear	Adequate
Jewsbury & Cooke 1977	Adequate	Unclear	Unclear	Unclear
Jinabhai *et al*. 2001	Unclear	Unclear	Unclear	Inadequate
Kardaman *et al*. 1985	Unclear	Unclear	Unclear	Adequate
King *et al*. 1988	Adequate	Unclear	Participants and care providers	Inadequate
King *et al*. 1989	Adequate	Unclear	Unclear	Inadequate
King *et al*. 2002	Adequate	Unclear	Assessors and clinicians	Inadequate
McMahon & Kolstrup 1979	Unclear	Unclear	Unclear	Inadequate
McMahon 1983	Unclear	Unclear	Unclear	Inadequate
Olds *et al*. 1999	Adequate	Adequate	Participants and assessors	Adequate
Omer 1981	Unclear	Unclear	Unclear	Inadequate
Oyediran *et al*. 1981	Unclear	Unclear	Unclear	Inadequate
Pugh & Teesdale 1983	Inadequate	Unclear	Participants, clinicians, and assessors	Adequate
Rey *et al*. 1983	Adequate	Unclear	Unclear	Adequate
Rey *et al*. 1984b	Unclear	Unclear	Unclear	Inadequate
Stephenson *et al*. 1985	Unclear	Unclear	Assessors	Unclear
Stephenson *et al*. 1989	Unclear	Unclear	Assessors	Adequate
Taylor *et al*. 1988	Unclear	Unclear	Assessors	Unclear
Wilkins & Moore 1987a	Adequate	Unclear	Assessors	Adequate

Effects of interventions

1. Metrifonate versus placebo

Four trials made this comparison (Jewsbury *et al*. 1977; Doehring *et al*. 1985; Stephenson *et al*. 1985; Stephenson *et al*. 1989).

Parasitological failure

Jewsbury *et al*. (1977) measured parasitological failure at one to three months and showed a marked effect in favour of metrifonate (RR 0.42, 95% CI 0.27 to 0.64; 64 participants, Analysis 1.1; see Appendix), but loss to follow up was high (44%). The effect also favoured metrifonate when failure was measured at three to 12 months in Jewsbury *et al*. 1977, Stephenson *et al*. 1985, and Stephenson *et al*. 1989 (RR 0.53, 95% CI 0.29 to 0.95; 680 participants, Analysis 1.1; see Appendix), although there was significant heterogeneity.

Loss to follow up was still high in Jewsbury *et al*. (1977), but less marked in the other two trials (Stephenson *et al*. 1985; Stephenson *et al*. 1989). In terms of differences in failure rates, there seemed to be an association with the level of endemicity: Jewsbury *et al*. (1977) and Stephenson *et al*. (1989 (high endemicity)) led to higher rates of failure at three to 12 months than Stephenson *et al*. (1985 (low endemicity)), but the lower dose used in Stephenson *et al*. (1989) may confound the observed higher failure rate. There was no obvious association of failure with age (all trials included children of up to 15 years) or follow up (all three trials measured failure at eight months).

Egg reduction rate

All four trials measured this at three to 12 months and demonstrated that metrifonate reduced egg excretion by over 90%. The placebo groups ranged from a 5.5% decrease to a 66.2% increase (Table 3.5).

Mean haemoglobin

Two trials (Stephenson *et al*. 1985) and (Stephenson *et al*. 1989), showed that participants in the metrifonate group had higher levels of mean haemoglobin than those in the placebo group (RR 0.30, 95% CI 0.28 to 0.32; 607 participants, Analysis 1.2; see Appendix).

Adverse events

Jewsbury *et al*. (1977) assessed adverse events and recorded none.

2. Praziquantel versus placebo

Eight trials made this comparison (McMahon & Kolstrup 1979; Oyediran *et al*. 1981; Doehring *et al*. 1985; Taylor *et al*. 1988; Stephenson *et al.* 1989; Befidi-Mengue *et al*. 1992; Olds *et al*. 1999; Borrmann *et al*. 2001).

Parasitological failure

Praziquantel (40 mg/kg x 1 oral) was superior to placebo at one to three months' follow up (RR 0.39, 95% CI 0.27 to 0.55; 534 participants, 4 trials, Analysis 2.1; see Appendix) and at three to 12 months (RR 0.23, 95% CI 0.14 to 0.39; 433 participants, 3 trials, Analysis 2.1; see Appendix). There was significant heterogeneity in the meta-analysis, possibly due to loss to follow up, which was high in McMahon & Kolstrup (1979 (31.6% and 36.9% for short and long follow-up times, respectively)), less than 10% for Stephenson *et al*. (1989), Olds *et al*. (1999), and Borrmann *et al*. (2001), and unreported in Taylor *et al.* (1988).

Egg reduction rate

Praziquantel had egg reduction rates of over 98% (geometric mean) in four trials and a 95% rate in Befidi-Mengue *et al*. (1992), and these were greater than those achieved with the placebo (5.3% to 64%). Doehring *et al*. (1985) reported a median reduction rate of 98.7% in the praziquantel group and 48.6% in the placebo group. The trials used different dosing schedules, but there was no clear relationship between the egg reduction rates and dosing schedules (Table 3.5).

Mean haemoglobin

Stephenson *et al*. (1989) reported a significant increase in mean haemoglobin with praziquantel (WMD 0.11, 95% CI 0.09 to 0.13; 209 participants, Analysis 2.2; see Appendix).

Adverse events

Olds *et al*. (1999) recorded 15% excess of mild to moderate adverse events with praziquantel compared with placebo, and Borrmann *et al*. (2001) reported combined events across comparison groups (127 mild and 6 moderate events); see Table 3.6. Neither trial recorded serious adverse events.

Table 3.5 Egg reduction rate: 1 to 12 months

Comparison (intervention vs control)	Dose		Geometric mean		Median		Trial
	Inter-vention	Control	Inter-vention	Control	Inter-vention	Control	
Metrifonate vs placebo	10 mg/kg x 2	Placebo	—	—	99.5%	48.6%	Doehring *et al*. 1985
	7.5 mg/kg x 3	"	—	—	91.3%	66.2% increase	Jewsbury & Cooke 1977
	7.5 mg/kg x 3	"	94%	12.7% increase	—	—	Stephenson *et al*. 1985
	10 mg/kg x 1	"	91.5%	5.3%	—	—	Stephenson *et al*. 1989
Praziquantel vs placebo	40 mg/kg x 1	Placebo	99.6%	5.3%	—	—	Stephenson *et al*. 1989
	40 mg/kg x 1	"	95%	64%	—	—	Befidi-Mengue *et al*. 1992
	40 mg/kg x 1	"	—	—	98.7%	48.6%	Doehring *et al*. 1985
	40 mg/kg x 1	"	98%	24%	—	—	Oyediran *et al*. 1981
	20 mg/kg x 2	"	99%	24%	—	—	"
	30 mg/kg x 1	"	86%	24%	—	—	"
	40 mg/kg x 1	"	98%	23.4%	—	—	Taylor *et al*. 1988
	30 mg/kg x 1	"	98.3%	23.4%	—	—	"
	20 mg/kg x 1	"	98.1%	23.4%	—	—	"
	40 mg/kg x 1	"	99.6%	20.3%	—	—	McMahon & Kolstrup 1979
	20 mg/kg x 2	"	99.8%	20.3%	—	—	"
	30 mg/kg x 1	"	99.6%	20.3%	—	—	"
Praziquantel plus albendazole	Praziquantel: 40 mg/kg Albendazole: 400 mg	Placebo	99%	12% increase	—	—	Beasley *et al*. 1999
	Praziquantel: 40 mg/kg Albendazole: 400 mg						
Metrifonate vs praziquantel	10 mg/kg x 2	40 mg/kg x 1	—	—	99.5%	98.7%	Doehring *et al*. 1985
	10 mg/kg x 3	"	98%	99%	—	—	McMahon 1983
	10 mg/kg x 1	"	96.3%	99.3%	—	—	Pugh & Teesdale 1983
	10 mg/kg x 1	"	91.5%	99.6%	—	—	Stephenson *et al*. 1989
	10 mg/kg x 1	"	80.3%	99%	—	—	Wilkins & Moore 1987a
Different metrifonate doses	10 mg/kg x 3	10 mg/kg x 1	88.7%	37.1%	—	—	Rey *et al*. 1984
	10 mg/kg x 2	"	81.9%	37.1%	—	—	"

Table 3.5 Continued

Comparison (intervention vs control)	Dose		Geometric mean		Median		Trial
	Inter-vention	Control	Inter-vention	Control	Inter-vention	Control	
Different praziquantel doses	30 mg/kg	40 mg/kg x 1	99%	99.2%	—	—	King *et al*. 1989
	20 mg/kg x 1	"	99%	99.2%	—	—	"
	20 mg/kg x 1	"	95%	98%	—	—	King *et al*. 2002
	2 x 20 mg/kg x 1	"	99.8%	99.6%	—	—	McMahon & Kolstrup1979
	30 mg/kg x 1	"	99.6%	99.6%	—	—	"
	2 x 20 mg/kg x 1	"	98.7%	97.7%	—	—	Oyediran *et al*. 1981
	30 mg/kg x 1	"	85.7%	97.7%	—	—	"
	30 mg/kg x 1	"	98.3%	98%	—	—	Taylor *et al*. 1988
	20 mg/kg x 1	"	98.1%	98%	—	—	"
Combination of metrifonate plus praziquantel	Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg x 1)	"	90%	99%	—	—	Wilkins & Moore 1987a

3. Artesunate versus placebo

One trial (Borrmann *et al*. 2001) which had two months' follow up, made this comparison.

Parasitological failure

There was no obvious benefit with artesunate (118 participants, Analysis 3.1; see Appendix).

Egg reduction rate

There was no significant difference in the egg reduction rate at two months' follow up (ERR_{log} 0.7 versus 0.4).

Haematuria

There was no clear difference between artesunate and placebo at two months (65% versus 53%).

Adverse events

Adverse events were reported as combined events (127 mild and six moderate events, Table 3.6) and not by comparison group. No serious adverse events were reported.

Table 3.6 Adverse events

Comparison	Trial	Drug (dose)	Adverse events	No. participants	Remarks
Vs placebo	Jewsbury & Cooke 1977	Metrifonate (7.5 mg/kg, 3 doses) Placebo	None reported	114	Investigated side effects as part of study, but none reported by participants
	Borrmann *et al*. 2001	Praziquantel (40 mg/kg, single) Artesunate 4 mg/kg/day/3 days Praziquantel (40 mg/kg) plus artesunate 4 mg/kg/day/3 days	6 moderate and 127 mild events	300	Mild events but equally distributed among treatment groups with abdominal pain (14%) and headache (12%) the most frequent
	Olds *et al*. 1999	Praziquantel (40 mg/kg, single dose) Praziquantel (40 mg/kg) plus albendazole (400 mg) Albendazole (400 mg)	15% 20% 14%	380	Adverse events mild to moderate
Metrifonate vs praziquantel	Wilkins & Moore 1987a	Praziquantel (40 mg/kg, 1 dose) Metrifonate (10 mg/kg, 1 dose)	See remarks	184	No serious adverse event. Commonly reported side effects included headache, weakness, dizziness, nausea/vomiting, diarrhoea, abdominal pain, general malaise, and fever. Among these events, abdominal pain, general malaise, and fever were reported more frequently in those treated with praziquantel, and others similar between groups

Table 3.6 Continued

Comparison	Trial	Drug (dose)	Adverse events	No. participants	Remarks
	McMahon 1983	Metrifonate (10 mg/kg, 3 doses) Praziquantel (30 mg/kg, single)	75% 30%	54	Adverse events were minor mostly abdominal pain but included nausea, vomiting, headache, fever, loose bowel, dizziness, itching, body pain
Metrifonate (different regimens)	Aden Abdi & Gustafsson1989	Metrifonate (7.5 mg/kg, 3 doses at 14-day intervals) Metrifonate (5 mg/kg given 3 times in 1 day)	7% 9%	201	Minor adverse events
Praziquantel (different doses)	Davis *et al*. 1981	Praziquantel (30 mg/kg, single) Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	19% 29% 17%	151	Minor events, mostly abdominal discomfort
	Kardaman *et al*. 1985	Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	See remarks	215	Minor adverse events, occurred slightly more with 20 mg/kg x 2 than single 40 mg/kg dose
	Oyediran *et al*. 1981	Praziquantel (30 mg/kg, single) Praziquantel (40 mg/kg, single) Praziquantel (20 mg/kg x 2)	3%	66	No serious adverse events, only 2 moderate events (umbilical pain) were recorded across all the dose categories. Adverse events were not reported separately for each dose category

4. Praziquantel plus artesunate versus placebo

One trial with two months' follow up made this comparison (Borrmann *et al*. 2001).

Parasitological failure

There was a clear difference between the combination and placebo for failure rates at two months (RR 0.24, 95% CI 0.15 to 0.38; 118 participants, Analysis 4.1; see Appendix).

Egg reduction rate

The egg reduction rate was high for the combination compared with placebo (ERR_{log} 1.9 versus 0.4).

Haematuria

The urine erythrocyte counts were similar for the combination and placebo (65% versus 53%).

Adverse events

There were 127 mild and six moderate adverse events reported, but they were not separated by intervention group (Table 3.6).

5. Praziquantel plus albendazole versus placebo

Three trials made this comparison (Beasley *et al*. 1999; Olds *et al*. 1999; Jinabhai *et al*. 2001).

Parasitological failure

Praziquantel plus albendazole significantly reduced parasitological failures compared to placebo (RR 0.45, 95% CI 0.35 to 0.59; 471 participants, 3 trials, Analysis 5.1; see Appendix). Jinabhai *et al*. (2001) which was conducted in a low-endemic area, showed a better effect compared with Beasley *et al*. (1999 (moderate and high endemicities)) or Olds *et al*. (1999 (very high endemicity)).

Egg reduction rate

Beasley *et al*. 1999 reported a geometric mean reduction rate of over 99% with the combination compared to a 12% increase with the placebo (Table 3.5).

Mean haemoglobin

Beasley *et al*. (1999) showed marked improvement in mean haemoglobin with the combination (WMD 0.24, 95% CI 0.22 to 0.26; 250 participants, Analysis 5.2; see Appendix).

6. Metrifonate versus praziquantel

Five trials made this comparison (McMahon 1983; Pugh & Teesdale 1983; Wilkins 1987a; King *et al*. 1988; Stephenson 1989).

Some early studies investigated a single dose of 10 mg/kg metrifonate (the standard dose is 7.5 to 10 mg/kg three times at 14-day intervals) with the standard single dose of 40 mg/kg praziquantel. Although the single metrifonate dose was

inferior in three trials measuring failure at one to 12 months, the 95% CI were too wide for statistical significance (RR 2.31, 95% CI 0.91 to 5.82; 462 participants, Figure 3.1), due to significant heterogeneity between the trials (I^2 93.9%). A possible association with follow-up time was found: Pugh & Teesdale 1983 (RR 1.26 at one month), Wilkins 1987a (RR 2.23 at three months), and Stephenson *et al*. 1989 (RR 4.62 at eight months).

There was no significant difference in failure when metrifonate (10 mg/kg three times at 14-day intervals) was compared with praziquantel (30 mg/kg) in a small trial involving 54 participants (McMahon 1983, Analysis 6.1; see Appendix). The metrifonate regimen was then changed to three doses of 10 mg/kg every four months for one year), and this resulted in effects similar to the standard 40 mg/kg of praziquantel (Figure 3.1).

Effect on light and heavy infections

One trial reported a subgroup analysis that showed that there was no significant difference between metrifonate (10 mg/kg every four months for one year) and praziquantel (40 mg/kg) curing light infections (626 participants, 1 trial, Analysis 7.1; see Appendix), but that this metrifonate dose was better at controlling heavy infections (615 participants, Analysis 7.2; see Appendix). Given that the subgroup was stratified after randomization, care should be taken in interpreting these results.

Egg reduction rate

Both metrifonate (two and three doses of 10 mg/kg) and praziquantel (single dose 40 mg/kg) led to reductions in egg excretion of over 98% in two trials (McMahon 1983; Doehring *et al*. 1985), while in three trials a single dose of metrifonate (10 mg/kg) also resulted in an egg reduction of over 90% (Pugh & Teesdale 1983; Wilkins & Moore 1987; Stephenson *et al.* 1989) (Table 3.5).

Mean haemoglobin

Stephenson *et al*. 1989 showed that participants in the metrifonate group had greater mean haemoglobin levels than those in the praziquantel group (RR 0.19, 95% CI 0.17 to 0.21; 208 participants, Analysis 6.2; see Appendix).

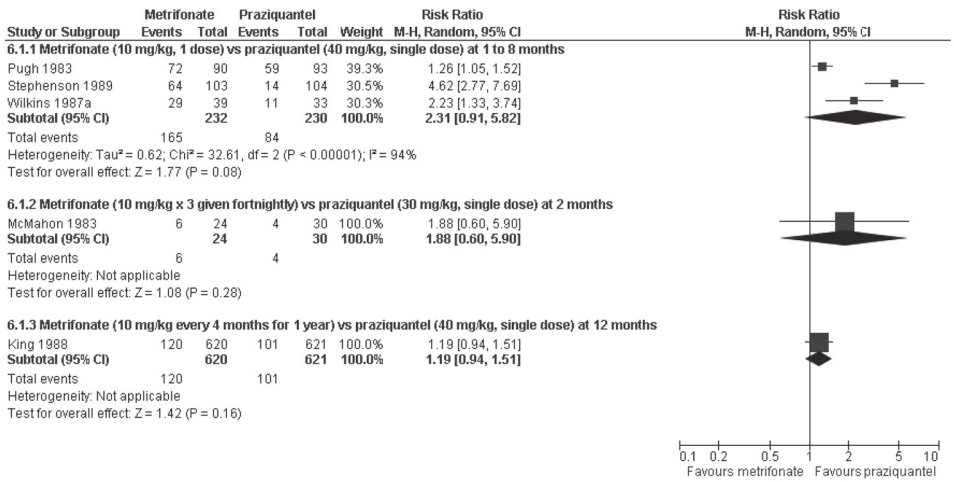

Figure 3.1 Metrifonate (different regimens) vs praziquantel (30 mg/kg or 40 mg/kg, single dose): Parasitological failure.

Adverse events

McMahon 1983 (54 participants) reported similar minor adverse events between metrifonate (10 mg/kg) and praziquantel (30 mg/kg), except for abdominal pain and vomiting, which occurred more frequently in the metrifonate group than the praziquantel group (40% versus 13% and 8% versus 0%). No serious adverse events were reported. Wilkins & Moore 1987 (184 participants) compared metrifonate (10 mg/kg x 1) versus praziquantel (40 mg/kg x 1) and reported no serious adverse event. Commonly reported adverse events for the combination treatment included headache, weakness, dizziness, nausea/vomiting, diarrhoea, abdominal pain, general malaise, and fever. Among these events, abdominal pain, general malaise, and fever were reported more frequently in those treated with praziquantel than metrifonate.

7. Metrifonate regimens: 5 mg/kg x 3, given in one day versus 7.5 mg/kg x 3, given fortnightly

One trial with 201 participants made this comparison (Aden Abdi & Gustafsson 1989).

Parasitological failure

There was no significant difference in parasitological failure (201 participants, Analysis 8.1; see Appendix).

Egg reduction rate

Egg reduction rate (geometric mean) was 96% for the one-day regimen versus 97% for the fortnightly regimen (Table 3.5).

Adverse events

There was little difference in the percentage of mild adverse events reported for the fortnightly regimen (7%) versus the one-day regimen (9%) (Table 3.6).

8. Metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg) versus praziquantel (40 mg/kg)

Wilkins & Moore 1987 showed that the combination was inferior to praziquantel at reducing parasitological failure (72 participants, Analysis 9.1; see Appendix). The same trial reported an egg reduction rate of over 90% for the combination therapy (Table 3.5).

9. Metrifonate (10 mg/kg x 1) versus metrifonate (10 mg/kg x 1) plus praziquantel (10 mg/kg)

Wilkins & Moore 1987 showed no significant difference in parasitological failures with the two interventions (78 participants, Analysis 10.1; see Appendix).

10. Artesunate plus praziquantel versus praziquantel alone

Borrmann *et al.* 2001 showed no statistically significant difference between the combination and single treatment for parasitological failure (177 participants, Analysis 11.1; see Appendix). There was no obvious difference in egg reduction rates (ERR_{log} 1.9 versus 1.2). The trial reported 127 mild and six moderate adverse events, but they were not reported by intervention group (Table 3.6).

11. Different metrifonate doses

Rey *et al*. 1984 compared three doses with one and two doses of 10 mg/kg metrifonate. There was no significant difference in the number of parasitological failure between two and three doses at one month and four months (Analysis 12.1; see Appendix). There were fewer parasitological failures with the three-dose regimen over the one-dose regimen at one month's follow up (RR 2.75, 95% CI 1.29 to 5.85; 93 participants) and four months' follow up (RR 1.52, 95% CI 1.03 to 2.25; 111 participants, Figure 3.2).

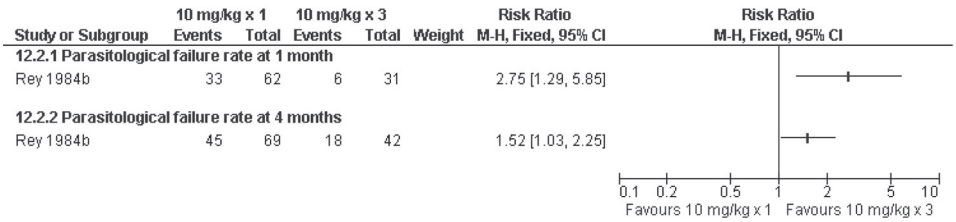

Figure 3.2 Metrifonate (10 mg/kg x 1) vs metrifonate (10 mg/kg x 3): Parasitological failure

12. Different praziquantel doses versus standard dose (40 mg/kg x 1 oral)

Ten trials compared the standard dose with various other doses (McMahon & Kolstrup 1979; Davis *et al*. 1981; Oyediran *et al*. 1981; Omer 1981; Rey *et al*. 1983; Kardaman *et al*. 1985; Wilkins & Moore 1987; Taylor *et al*. 1988; King *et al*. 1989; King *et al*. 2002).

Parasitological failure

There was no significant difference between the standard dose and 20 mg/kg x 2 (4 trials, Figure 3.3), 30 mg/kg (6 trials, Figure 3.4), and 20 mg/kg dose (2 trials, Figure 3.5); these results were similar for follow up at one, three, and six months.

Losses to follow up were generally high in some trials, but these did not differ across treatment and control groups within a single trial. There was no significant heterogeneity between the trials, and background endemicities did not seem to play a role; all trial sites had high endemicities except the trial by Davis *et al*. 1981 (not specified). Examining for a differential effect between heavy and moderate or light infections with 30 mg/kg versus 40 mg/kg, a subgroup analysis of one small trial did not demonstrate a difference (116 participants, King *et al*. 1989, Analysis 13.5; see Appendix). Here caution should be exercised in the interpretation of the data since the subgroup was selected after randomization.

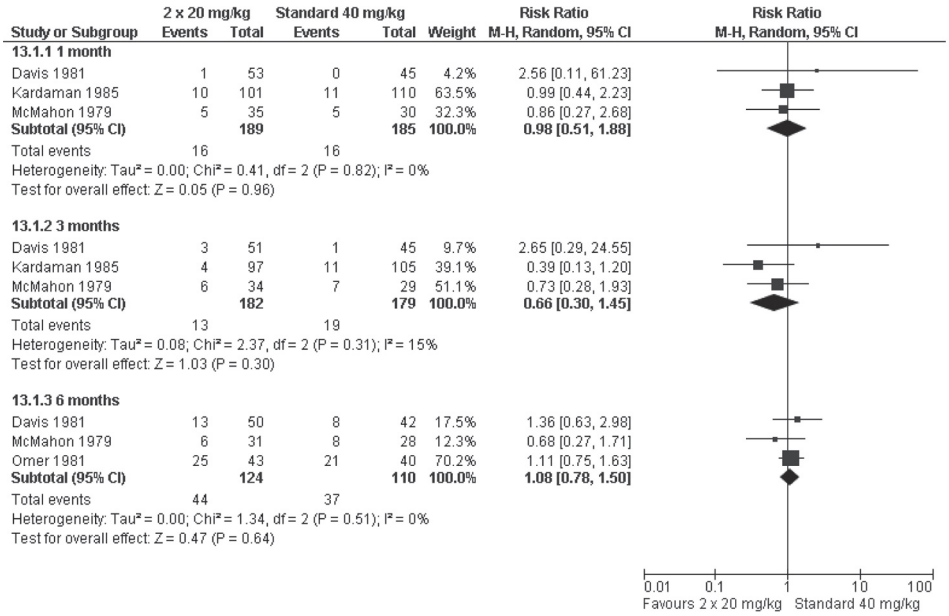

Figure 3.3 Praziquantel (2 x 20 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure.

Egg reduction rate

Five trials all showed no apparent differences in egg reduction rate (geometric mean); all had greater than 95% reduction in both arms, except for Oyediran *et al*. (1981) in which the 30 mg/kg dose gave an 85.7% reduction compared with 97.7% for the standard dose (Table 3.5).

Haematuria

Two trials measured haematuria (King *et al*. 1989; King *et al*. 2002). King *et al*. 1989 (117 participants) showed no difference in the rate of clearance between 30 mg/kg x 1 and the standard 40 mg/kg x 1 dose at three months (100% versus 99%). However, King *et al*. 2002 (200 participants) showed a clear difference at six weeks' follow up between 20 mg/kg x 1 and the standard 40 mg/kg x 1 (40% versus 63%).

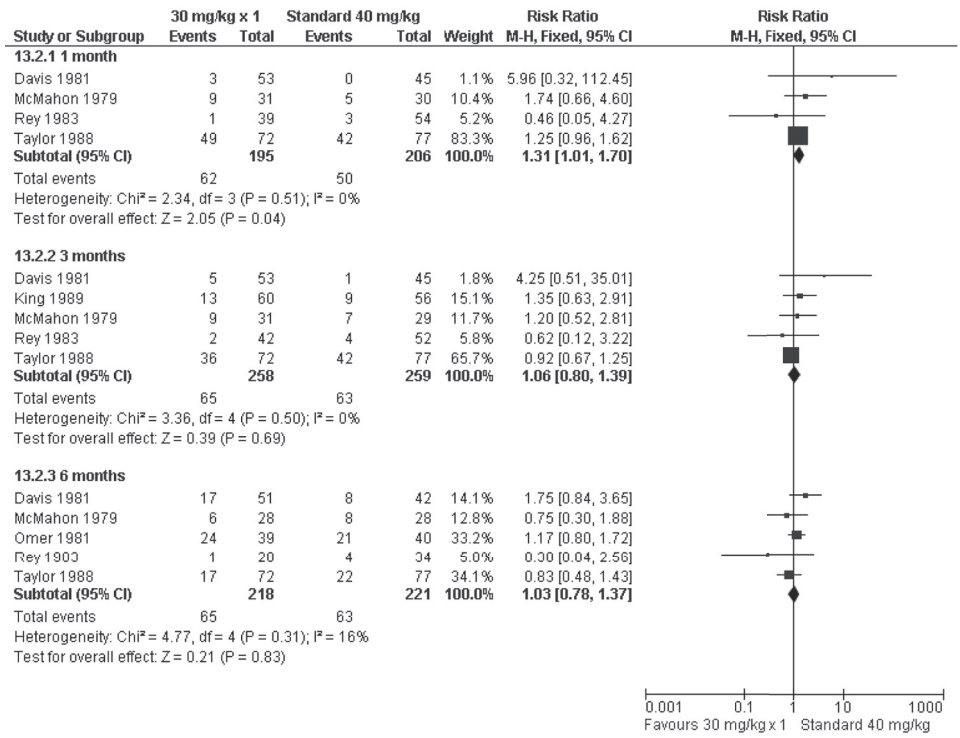

Figure 3.4 Praziquantel (30 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure.

Adverse events

Davis *et al*. 1981 recorded similar numbers of mild adverse events for each dose: 19%, 29%, and 17% for 30, 40, and 20 mg/kg x 2, respectively. Kardaman *et al*. (1985) reported slightly higher rates with 20 mg/kg x 2 than the single dose of 40 mg/kg, but no numbers were reported. Neither trial reported serious adverse events (Table 3.6). Oyediran *et al*. (1981) reported combined adverse events across 40, 30, and 20 mg/kg and recorded only two moderately severe events (umbilical pain). No serious adverse events were recorded.

Some Tables and Analyses (Figures) are not reported here but can be found in the Appendix.

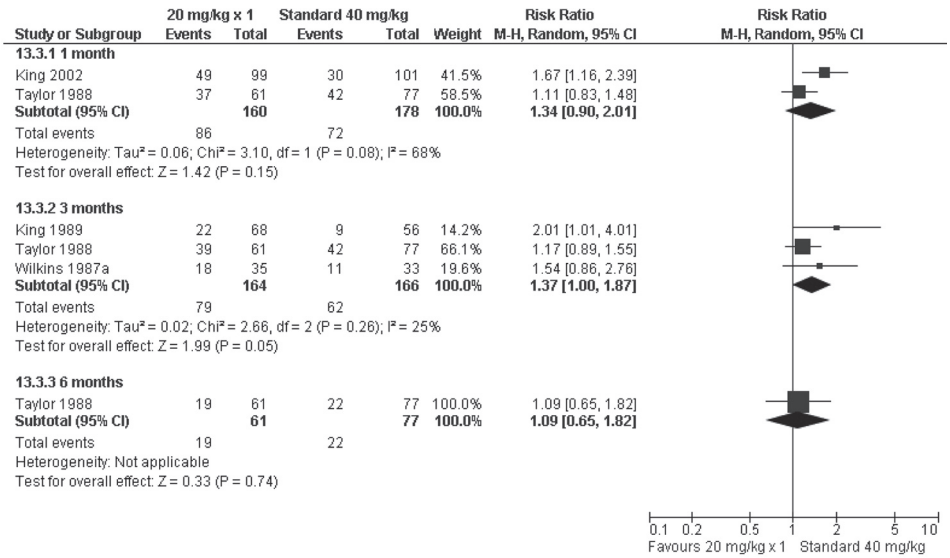

Figure 3.5 Praziquantel (20 mg/kg) vs praziquantel (standard 40 mg/kg): Parasitological failure

3.7 Discussion

Most of the 24 included trials were conducted many years ago, mostly in the 1970s and 1980s, and thus the standards of methodological quality did not reach the high standards that we would expect from trials carried out today; for example, only four out of the 24 trials used adequate methods to conceal allocation. However, effect sizes are so marked that it is unlikely that methodological quality will have caused such substantive biases to interfere with the marked effects and differences reported.

Both metrifonate and praziquantel showed good effects, but no trial compared the standard dose of each drug in a head-to-head comparison; instead trials compared different doses of each. Given that no trial compared the standard dose of metrifonate (7.5 to 10 mg/kg 3 times at 14-day intervals) with that of praziquantel (40 mg/kg) in a head-to-head assessment, discussion of adherence to treatment from currently available data is limited. However, the failure rate with the recommended standard dose of metrifonate (7.5 to 10 mg/kg 3 times at 14-day intervals) is 19% to 48%, while that of praziquantel (single 40 mg/kg oral dose) is 0% to 37% at one to three months' follow up. A dose of 7.5 mg/kg metrifonate produced more failures than 10 mg/kg, both doses administered three times at 14-day intervals. There appears to be no

difference in effects of metrifonate 10 mg/kg given every four months for one year and the standard dose of praziquantel (40 mg/kg), but this may not be conclusive as the evidence came from only one trial (King *et al*. 1988). Metrifonate (10 mg/kg 3 times at 14-day intervals) showed a similar effect to praziquantel (30 mg/kg). Public health programmes often recommend multiple-dose regimens, such as for metrifonate (3 doses of 7.5 to 10 mg/kg administered once every 14 days or every 4 months), but these are difficult to implement and might compromise overall compliance.

Both metrifonate and praziquantel showed high degrees of uncertainty around their effect estimates as shown by the wide confidence intervals. The small numbers in some of the trials may explain the levels of uncertainty. In this review we have analysed data mainly around infectivity and assumed statistical significance to be equal to clinical significance because it is not likely that small differences in effect of drugs being evaluated can mean large risks or clinical effects.

A single dose of 20 or 30 mg/kg of praziquantel was similarly efficacious compared to the standard dose of 40 mg/kg in terms of all outcomes measured in this review. Given current emphasis on controlling morbidity in high burden areas and morbidity, especially in children, is associated with the number of eggs in an individual (WHO 2002), this finding suggests lower doses of praziquantel may be effective in morbidity control. However, these results should be considered with caution. While it is true that parasite load (expressed by egg counts) is an important factor in both morbidity for the individual patient and environmental contamination (WHO 2002), a sub-curative dose may unduly put the drug under selective pressure and favour parasite resistance (Doenhoff 1998). Pharmacokinetic data of different doses of praziquantel are few and old, and have been obtained in healthy volunteers rather than in patients with schistosomiasis (Leopold *et al*. 1978). An exponential increase was found in the area under the curve (AUC) with the praziquantel dose in the range of 5 to 50 mg/kg, with a six-fold increase from 20 to 50 mg/kg (Leopold *et al*. 1978). However, these data do not come from infected patients, and hence cannot be extrapolated so easily. The artemisinins, best known for their use as antimalarial drugs, have been found to be effective against immature schistosomes in laboratory studies (Utzinger *et al.* 2001a; Utzinger *et al*. 2001c; Utzinger *et al*. 2002). However, results from one low-quality trial show that artesunate is not effective when used alone or when combined with praziquantel. This may, to some extent, be explained by the fact that mature worms are less sensitive to the artemisinins (Utzinger *et al*. 2007).

It has been suggested that there is a significant infection-associated loss of performance in a person with schistosomiasis that can be improved through antischistosomal treatment (Bergquist *et al*. 2005; King *et al*. 2005). This would necessitate any comprehensive assessment of antischistosomal drugs to include

outcomes of subtle disease such as resolution of bladder or urinary tract pathology, growth, physical fitness, cognitive function, and educational achievement. Most trials did not investigate these outcome measures because the focus tended to be on measures of infectivity. However, we may include functional outcome measures in future updates if trials provide comprehensive data.

Adverse events

The rationale behind the widely spaced dosing interval of metrifonate treatment derives from its long-lasting effect on red blood cells and plasma cholinesterases (Plestina *et al*. 1972). However, the clinical significance of this effect and why adverse events disappear during the first 12 to 24 hours but the recovery of the enzymes takes more than four to six weeks is not known (Plestina *et al*. 1972). Safety studies have shown no serious adverse events in patients treated with 5 to 10 mg/kg metrifonate daily for six to 12 days (Snellen 1981), and various reviews of metrifonate's toxicology and pharmacology during its extensive use for urinary schistosomiasis in the 1970s concluded that it had very few adverse events (Holmstedt *et al*. 1978). Also, metrifonate is currently used in Alzheimer's disease, which requires a high dose and extended regimen, and a systematic review has concluded an overall good tolerability with only mild to moderate adverse events (López-Arrieta & Schneider 2006). In the current review, although adverse events were generally poorly assessed in the few trials measuring this, no trial recorded a serious adverse event, and no significant differences in the number and type of adverse events between metrifonate and praziquantel were recorded, except for abdominal pain where greater numbers of participants in the metrifonate group were reported with this adverse event.

3.8 Authors' conclusions

Implications for practice

Both praziquantel and metrifonate are efficacious (with few adverse events) for treating urinary schistosomiasis, but metrifonate requires multiple administrations and hence is operationally less convenient and more costly in community-based control programmes. However, leaving praziquantel as the only antischistosomal drug raises considerable concern in case resistance develops against this drug. We suggest metrifonate be reconsidered for the WHO Model List of Essential Medicines.

Implications for research

Well-designed trials are required to investigate the following areas.

- Different doses and regimens of metrifonate to identify appropriate doses for treatment and to facilitate adherence.
- Evaluation of the artemisinins (results are only available for artesunate and these are inconclusive).
- Combination therapy, ideally with drugs with unrelated mechanisms of action and targeting the different developmental stages of the schistosomes in the human host should be pursued; for example, praziquantel plus metrifonate, and praziquantel plus an artemisinin derivative.

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Appendix

For Appendix please refer to the main Cochrane review at:

http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000053/pdf_fs.html

Chapter 4

Treatment of urinary *schistosomiasis*: methodological issues and research needs identified through a Cochrane systematic review

Danso-Appiah A, Garner P, Olliaro PL, Utzinger J. Treatment of urinary schistosomiasis: methodological issues and research needs identified through a Cochrane systematic review *Parasitology* 2009;136:1-13

4.1 Abstract

Guidelines recommend praziquantel (PZQ) for the treatment and control of schistosomiasis, with no real alternative. Metrifonate was still widely used against *Schistosoma haematobium* in the 1990s, and then withdrawn. Experimental studies and clinical trials suggest that artemisinin compounds are active against *S. haematobium*. In a Cochrane systematic review assessing the efficacy and safety of drugs for treating urinary schistosomiasis, 24 randomized controlled trials (n=6315 individuals) met our inclusion criteria. These trials compared a variety of single agent and combination regimens with PZQ, metrifonate or artemisinin derivatives. The review confirmed that both the standard recommended doses of PZQ (single 40 mg/kg oral dose) and metrifonate (3x7.5–10 mg/kg oral doses administered fortnightly) are efficacious and safe in treating urinary schistosomiasis, but there is no study comparing these two regimens head-to-head. There is currently not enough evidence to evaluate artemisinin compounds. Most of the studies included in the Cochrane systematic review were insufficiently powered, lacked standardization in assessing and reporting outcomes, and had a number of methodological limitations. In this paper we discuss the implications of these findings with respect to public health and research methodology and propose priority research needs.

4.2 Introduction

Schistosomiasis is a common parasitic disease in the tropics and subtropics. An estimated 779 million individuals are at risk of acquiring schistosomiasis and more than 200 millions were infected in mid-2003 (Steinmann *et al*. 2006). The World Health Organization (WHO) estimates that the global burden due to schistosomiasis may be as high as 4.5 million disability-adjusted life years (DALYs) (WHO, 2002). However, a meta-analysis suggests that disability weights might be 2–15 times higher than those used in the global burden of disease study (King *et al*. 2005), and that the DALY underestimates the importance of chronic diseases like schistosomiasis (King & Bertino 2008). This is further substantiated by the results of approaches using a quality of life questionnaire and decision-tree modelling (Jia *et al*. 2007; Finkelstein *et al*. 2008). From a public health perspective, the three most important schistosome species are *Schistosoma haematobium* (causing urinary schistosomiasis), and *S. mansoni* and *S. japonicum* (causing intestinal schistosomiasis).

Two drugs, metrifonate and praziquantel (PZQ), have been used extensively for urinary schistosomiasis (Cioli *et al*. 1995; Utzinger & Keiser 2004). However, in the late 1990s, metrifonate was withdrawn from the WHO model list of essential medicines because it was considered clinically, economically and operationally inferior to PZQ as it is only active against *S. haematobium*, requires multiple administrations, and hence is less convenient in large-scale control programmes (Feldmeier & Chitsulo 1999). Thus, PZQ remains the only drug for clinical management and community-based control of schistosomiasis (Cioli 2000; Fenwick *et al*. 2003; Utzinger & Keiser 2004; Caffrey 2007; Doenhoff *et al*. 2008). Large-scale morbidity control programmes became feasible as the price of PZQ fell from approximately US$ 1.0 in the 1980s to less than US$ 0.1 per 600 mg tablet (Fenwick *et al*. 2003; Fenwick *et al*. 2006; Doenhoff *et al*. 2008). Paradoxically, this also stalled investments in the discovery and development of alternative control measures, such as other drugs, vaccines and diagnostics (Utzinger *et al*. 2007; Bergquist *et al*. 2008). Research carried out over the past 15 years revealed the antischistosomal properties of artemisinin derivatives, which act especially on the young developing stages of the parasites (for a recent review see Utzinger *et al*. 2007) as opposed to PZQ, which acts against the adult worms and the very young schistosomula just after skin penetration (Sabah *et al*. 1986; Utzinger *et al*. 2007).

The use of PZQ has increased considerably after the 54th World Health Assembly set the target of at least 75% of school-aged children and other high risk groups to be treated regularly with PZQ by 2010 in areas where the disease is highly endemic (WHO, 2002). At least 17 million doses of PZQ have been administered, primarily to school-

aged children in selected African countries, since the launch of the 'Schistosomiasis Control Initiative' in 2003 (Fenwick *et al*. 2006). Relying on Praziquantel alone for controlling a disease that affects millions of people is risky should resistance develop against this drug (Danso-Appiah & de Vlas, 2002; Doenhoff *et al*. 2008).

In the light of this, we assessed the effects of PZQ and other antischistosomal treatments by conducting a Cochrane systematic review, including comparisons between PZQ and metrifonate and trials of combination treatments. During this process, we identified a number of methodological issues relevant to the interpretation of existing data that might help researchers to design more appropriate trials in the future. The full review is available on the Cochrane ibrary (Danso-Appiah *et al*. 2008). In this paper we highlight key findings of the review, discuss implications of various methodological limitations and consider future research needs.

4.3 Summary of Cochrane systematic review

Inclusion criteria and search strategy

To qualify for inclusion, a study was (1) to be controlled, randomized or quasi-randomized, enrolling individuals infected with *S. haematobium*, as determined microscopically for *S. haematobium* eggs in a standard filtrate of 10 ml of urine or by haematuria (Feldmeier & Poggensee 1993); and (2) to treat patients with either PZQ, metrifonate or artemisinin derivatives. An extensive, standard search was carried out, which included MEDLINE (1966 to August 2007), EMBASE (1974 to August 2007), LILACS (1982 to August 2007), conference proceedings and contacting specialists in the field (Danso-Appiah *et al*. 2008).

Data retrieval, quality assessment and analysis

Eligibility and methodological quality of the identified trials were assessed by the authors and the data analysed using Review Manager 4.2 (The Cochrane Collaboration, 2003). The main outcome measure was failure rate (the proportion of individuals remaining positive for eggs in their urine at follow-up). Comparisons between groups were expressed as relative risk (RR) with 95% confidence intervals (CIs) for both individual studies and on aggregate. The secondary parameter was egg reduction rate and was analysed using weighted mean difference with standard error. The proportion of patients with adverse events was compared between treatment and control arms.

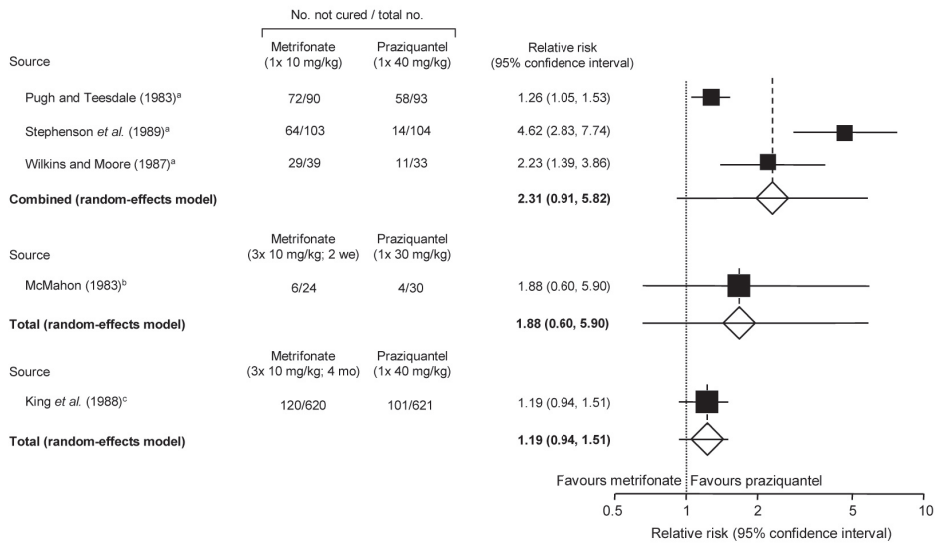
Key findings of the Cochrane systematic review

The search identified 24 randomised controlled trials that together involved 6315 participants. Table 4.1 summarises key characteristics of these 24 trials. When used as monotherapy, both metrifonate and PZQ showed obvious benefit in terms of parasitological outcomes (Danso-Appiah *et al*. 2008). One trial (120 participants) of artesunate showed no obvious benefit over placebo.

For combination treatments, one trial studied the combination of PZQ with artesunate, but there was no obvious advantage over PZQ alone.

Metrifonate versus PZQ: comparisons and dose effects

Figure 4.1 summarises the failure rate of metrifonate versus PZQ in the five trials meeting our inclusion criteria (McMahon 1983; Pugh & Teesdale 1983; Wilkins & Moore 1987; King *et al*. 1988; Stephenson *et al*. 1989).



[a] Evaluation 1-8 mo post-treatment; [b] Evaluation 2 mo post-treatment; [c] Evaluation 12 mo post-treatment

Figure 4.1 Risk ratio estimates (combined or total) of randomized controlled trial(s) of metrifonate (different regimens) versus PZQ (single dose, 30 mg/kg or 40 mg/kg) against S. haematobium. Rectangles represent risk ratios and sizes of the rectangles denote the weight given to each trial in the meta-analysis. Diamond and vertical broken line indicate combined (total) relative risk (RR). Horizontal lines indicate 95% confidence intervals. The dashed vertical line is the null value (RR=1; neither favouring metrifonate nor PZQ). Abbreviations: mo, month; we, week.

Table 4.1 Summary of the characteristics of randomised controlled trials included in our Cochrane systematic review (Danso-Appiah et al. 2008; Chapter 3 of this thesis) evaluating.

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Aden Abdi and Gustafsson (1989); Somalia	Not reported	5	Children: mean age of 14 years	Urine filtration (10 ml; 1 specimen)	Very high	300	1. Metrifonate (7·5 mg/kg × 3 given at 2-week intervals) 2. Metrifonate (5 mg/kg × 3 given in 1 day)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer)	1, 2, 3 and 6	Adequate	Adequate	Investigators, participants and assessors	33% at 2 months
Beasley *et al.* (1999); Tanzania	1994	1	Children: 7–12 years	Urine filtration (10 ml; 1 specimen)	High (56%)	357	1. PZQ (40 mg/kg × 1) plus albendazole (400mg × 1) 2. Placebo	1. Cure rate 2. Egg reduction rate 3. Mean haemo-globin	PZQ (Biltricide, Bayer)	3·75	Adequate	Unclear	Outcome assessors	30%
Befidi-Mengue *et al.* (1992); Cameroon	Not reported	1	Boys: 6–15 years	Urine filtration (10 ml; 1 specimen)	Not reported	436	1. PZQ (40 mg/kg × 1) 2. Placebo	1. Anaemia 2. Physical growth 3. Haematuria 4. Proteinuria	Not stated	6	Unclear	Unclear	Unclear	Unclear
Borrmann *et al.* (2001); Gabon	Not reported	3	Children: 5–13 years	Urine filtration (10 ml; 2 specimens)	Very high (80%)	300	1. PZQ (40 mg/kg × 1) 2. Artesunate (4 mg/kg/day for 3 days) 3. PZQ (40 mg/kg × 1) plus artesunate (4 mg/kg/day over 3 days) 4. Placebo	1. Cure rate 2. Adverse events 3. Resolution of haematuria 4. Egg reduction rate	Not stated	8	Adequate	Adequate	Participants and investigators	1·3%
Davis *et al.* (1981); Zambia	Not reported	1	Children and young adults: 7–22 years	Urine filtration (10 ml; 3 specimens)	Not reported	79	1. PZQ (20 mg/kg × 1) 2. PZQ (30 mg/kg × 1) 3. PZQ (40 mg/kg × 1) 4. PZQ (20 mg/kg × 2) 5. Placebo	1. Adverse events 2. Cure rate 3. Mean haemoglobin	Not stated	1, 6, 9 and 12	Adequate	Adequate	Participants, investigators and outcome assessors	7·6% and 16·5% at 6 and 12 months, respectively
Doehring *et al.* (1985); Sudan	Not reported	1	Boys: 6–13 years	Urine filtration (10 ml; 3 specimens)	Very high	182	1. PZQ (40 mg/kg × 1) 2. Metrifonate (10 mg/kg × 3 given at 2-week intervals) 3. Placebo	1. Egg reduction rate 2. Proteinuria	Not stated	1	Unclear	Unclear	Unclear	0%
Jewsbury and Cooke (1976); Zimbabwe	Not reported	4	Children (age not specified)	Urine filtration (10 ml; 1 specimen *vs.* 3 specimens)	Very high (80%)	179	1. Metrifonate (7·5 mg/kg × 3 given at 2-week intervals) 2. Placebo (Third arm excluded from current review)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer)	1·2, 7 and 16	Adequate	Unclear	Unclear	Not reported
Jinabhai *et al.* (2001); South Africa	Not reported	11	Children: 8–10 years	Not stated	High	268	1. PZQ (40 mg/kg × 1) plus albendazole (400 mg × 1) 2. Placebo (Another arm consisted of albendazole (400 mg × 1) for intestinal helminths)	1. Cure rate	Not stated	4	Unclear	Unclear	Unclear	Not reported

Table 1. (*cont.*)

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Kardaman *et al.* (1985); Sudan	Not reported	Not reported	Children: 7–11 years	Urine filtration (10 ml; 2 specimens)	Not reported	237	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 2)	1. Adverse events 2. Cure rate 3. Egg reduction rate	Not reported	1, 3, 6 and 12	Unclear	Unclear	Unclear	7·3%
King *et al.* (1988); Kenya	Not reported	Not reported	Children and young adults: 4–21 years	Urine filtration (10 ml; 2 specimens)	Not reported	2628	1. Metrifonate (10 mg/kg × 3 given at 4-month intervals) 2. PZQ (40 mg/kg × 1)	1. Haematuria 2. Proteinuria (Other arms not relevant for current review, hence were excluded)	Metrifonate (Bilarcil, Bayer); PZQ (Biltricide Bayer)	12	Adequate	Unclear	Participants and assessors	23%
King *et al.* (1989); Kenya	Not reported	Not reported	Children and adults (age not specified)	Urine filtration (10 ml; 2 specimens)	Very high	280	1. PZQ (40 mg/kg × 1) 2. PZQ (30 mg/kg × 1) 3. PZQ (20 mg/kg × 1) 4. PZQ (10 mg/kg × 1)	1. Cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria	Not reported	3	Adequate	Unclear	Unclear	14%
King *et al.* (2002); Kenya	1993	2	Children and young adults: 4–23 years	Urine filtration (10 ml; 2 specimens)	Very high (80%)	291	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 1)	1. Cure rate 2. Egg reduction rate 3. Haematuria 4. Proteinuria	Not reported	2·5 and 9	Adequate	Unclear	Clinicians and assessors	31%
McMahon and Kolstrup (1979); Tanzania	Not reported	1	Children: 7–15 years	Urine filtration (10 ml; 3 specimens)	Not reported	183	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2) 4. Placebo	1. Cure rate 2. Egg reduction rate 3. Adverse events	PZQ (Biltricide, Bayer)	1, 3 and 6	Unclear	Unclear	Unclear	31%, 32% and 36% at 1, 3 and 6 months, respectively
McMahon (1983); Tanzania	Not reported	1	Children and adults (age not specified)	Urine filtration (10 ml; 3 specimens)	Not reported	90	1. Metrifonate (10 mg/kg × 3 given at 2-week intervals) 2. PZQ (30 mg/kg × 1) (Third arm consisting of niradazole was excluded)	1. Cure rate 2. Egg reduction rate 3. Adverse events	Not reported	2 and 4	Unclear	Unclear	Unclear	14% and 31% at 2 and 4 months, respectively
Olds *et al.* (1999); Kenya	Not reported	1	Children: 4–18 years	Urine filtration (10 ml; 2 specimen *vs.* 10 ml; 1 specimen)	Very high	380	1. PZQ (40 mg/kg × 1) plus albendazole (400 mg × 1) 2. PZQ plus albendazole placebo 3. Albendazole plus PZQ placebo 4. Both placebos	1. Physical growth 2. Haemoglobin 3. Failure rate 4. Egg reduction rate 5. Adverse effects	Not reported	1·5, 3, 6 and 12	Adequate	Adequate	Participants and assessors	1%, 1%, 10% and 17% at 1·5, 3, 6 and 12 months, respectively
Omer (1981); Sudan	1978–79	1	Children (>8 years) and adults	Urine filtration (10 ml; 1 specimen)	Very high	153	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2)	1. Adverse events 2. Cure rate 3. Egg reduction rate	PZQ (Biltricide, Bayer)	6	Unclear	Unclear	Unclear	20%
Oyediran *et al.* (1981); Nigeria	Not reported	1	Children: 9–16 years	Urine filtration (10 ml; 3 specimens)	Light to moderate	90	1. PZQ (30 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. PZQ (20 mg/kg × 2) 4. Placebo	1. Egg reduction rate 2. Adverse events	PZQ (Biltricide, Bayer)	1, 3 and 6	Unclear	Unclear	Unclear	31·7%, 32·3% and 36% at 1, 3 and 6 months, respectively

Table 1. (*cont.*)

Reference and country where trial was implemented	Year trial was conducted	N*	Age of participants	Diagnostic approach**	Endemicity (prevalence)	Sample size	Intervention	Outcome measures	Brand of drug	Follow-up (months)	Quality assessment			
											Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow-up
Pugh and Teesdale (1983); Malawi	Not reported	Not reported	Children: 5–18 years	Urine filtration (10 ml; 1 specimen)	Not reported	600	1. PZQ (40 mg/kg × 1) 2. Metrifonate (10 mg/kg × 1) 3. Placebo	1. Cure rate 2. Egg reduction rate 3. Adverse events	Metrifonate (Bilarcil, Bayer); PZQ (Biltricide, Bayer)	1, 3 and 6	Inadequate	Unclear	Participants, clinicians and assessors	3% at 1 month
Rey *et al.* (1983); Niger	Not reported	3	Children and adults (age not specified)	Urine filtration (10 ml; 1 specimen)	High (50%)	103	1. Metrifonate (10 mg/kg × 1) 2. Metrifonate (10 mg/kg × 2 given fortnightly) 3. Metrifonate (10 mg/kg × 3 given fortnightly)	1. Cure rate 2. Egg reduction rate	Not reported	1, 3 and 6	Adequate	Unclear	Unclear	9·7%, 6·4% and 8·1% at 1, 3 and 6 months, respectively
Rey, Nouhou and Sellin (1984); Niger	Not reported	3	Children and adults (age not specified)	Urine filtration (10 ml; 1 specimen)	Not reported	286	1. Metrifonate (10 mg/kg × 1) 2. Metrifonate (10 mg/kg × 2 given fortnightly) 3. Metrifonate (10 mg/kg × 3 given fortnightly)	1. Cure rate 2. Egg reduction rate	Not reported	2 and 4	Unclear	Unclear	Unclear	50% and 38·8% at 2 and 4 months, respectively
Stephenson *et al.* (1985); Kenya	Not reported	1	Children: 6–15 years	Urine filtration (10 ml of urine adjusted for whole volume)	Moderate (46%)	400	1. Metrifonate (7·5 mg/kg × 3 given fortnightly) 2. Placebo	1. Cure rate 2. Splenomegaly 3. Hepatomegaly 4. Egg reduction rate 5. Haemoglobin 6. Anthropometric measurements	Not reported	8	Unclear	Unclear	Assessors	Not reported
Stephenson *et al.* (1989); Kenya	Not reported	Not reported	Children (age not specified)	Urine filtration (10 ml of urine adjusted for whole volume)	Light to moderate	347	1. Metrifonate (10 mg/kg × 1) 2. PZQ (40 mg/kg × 1) 3. Placebo	1. Cure rate 2. Egg reduction rate 3. Physical growth	Not reported	8	Unclear	Unclear	Assessors	10%
Taylor, Murare and Manomano (1988); Zimbabwe	Not reported	1	Children: 10–15 years	Urine filtration (10 ml; 3 specimens)	Very high (77%)	373	1. PZQ (10 mg/kg × 1) 2. PZQ (20 mg/kg × 1) 3. PZQ (30 mg/kg × 1) 4. PZQ (40 mg/kg × 1) 5. Placebo	1. Cure rate 2. Egg reduction rate	Not reported	1, 3 and 6	Unclear	Unclear	Assessors	No losses reported
Wilkins and Moore (1987); Gambia	Not reported	3	Children: 2–19 years	Urine filtration (10 ml; 3 specimens)	Very high	184	1. PZQ (40 mg/kg × 1) 2. PZQ (20 mg/kg × 1) 3. PZQ (10 mg/kg × 1) 4. Metrifonate (10 mg/kg × 1) 5. Metrifonate (10 mg/kg × 1) plus PZQ (10 mg/kg × 1)	1. Egg reduction rate 2. Adverse events	Not reported	3	Adequate	Unclear	Assessors	No losses reported

* N – Number of communities involved in the trial.

** For urine filtration, 10 ml; 3 specimen *vs.* 10 ml; 1 specimen means pre- and post-treatment diagnosis varied; i.e. pre-treatment diagnosis involved 10 ml and 3 specimen but 10 ml and 1 specimen for post-treatment assessment.

* N – Number of communities involved in the trial.

** For urine filtration, 10 ml; 3 specimen vs. 10 ml ; 1 specimen means pre- and post-treatment diagnosis varied; i.e. pre-treatment diagnosis involved 10 ml and 3 specimen but 10 ml and 1 specimen for post-treatment assessment.

When metrifonate was introduced, some early studies investigated a single dose of 10 mg/kg (the standard dose is 7.5 to 10 mg/kg three times at 14-day intervals) versus the standard single dose of 40 mg/kg PZQ. Although the single metrifonate dose was inferior in three trials measuring failure at one to eight months, the 95% CIs were too wide for statistical significance (RR=2.31, 95% CI: 0.91–5.82; n=462 participants). This lack of significance is due to significant heterogeneity between trials (I^2=94%) likely to be associated with the duration of follow-up: the RR was 1.26 at one month of follow-up (Pugh & Teesdale 1983), 2.23 at three months (Wilkins and Moore, 1987) and 4.62 at eight months (Stephenson *et al*. 1989).

There was no significant difference in failure rates when metrifonate given as multiple doses (3 x 10 mg/kg fortnightly) was compared with PZQ (30 mg/kg) in a small trial involving 54 participants (McMahon 1983). A trial comparing three doses of metrifonate at 10 mg/kg given once every four months with the standard 40 mg/kg PZQ (single dose) in school-aged children in Kenya detected no difference overall, but metrifonate was superior in the subgroup of children with a heavy infection (RR=0.88, 95% CI: 0.80–0.96; n=615 participants). However, as the subgroup was stratified after randomisation, this result should be interpreted with caution. Both metrifonate (two and three doses of 10 mg/kg) and PZQ (single dose 40 mg/kg) led to very high reductions in egg excretion (>98%) in two trials (McMahon 1983; Doehring *et al*. 1985).

One trial (n=54 participants) compared adverse events and reported similar minor events between metrifonate (3 x 10 mg/kg) and PZQ (30 mg/kg); no serious adverse events were noted (McMahon 1983). Mild and transient abdominal pain was more common with triplicate metrifonate than single dose PZQ (75% versus 30%), but the dose of PZQ used (30 mg/ kg) was lower than the one currently recommended (40 mg/kg) (WHO 2002).

Metrifonate: dose comparisons

One trial with 201 participants compared 3 x 5 mg/kg metrifonate administered in a single day to 3 x 7.5 mg/kg given fortnightly (Aden Abdi & Gustafsson 1989).There was no significant difference in parasitological failure and egg reduction rate ; the geometric mean egg reduction rate was 96% for the one-day regimen and 97% for the fortnightly regimen. There was little difference in the percentage of patients with mild adverse events reported for the fortnightly regimen (7%) versus the one-day regimen (9%).

Three doses of metrifonate (10 mg/kg) were compared with one and two doses (Rey *et al*. 1984). There was no significant difference in parasitological failure rates between two and three doses at one month and four months follow-up. Similarly, no

significant differences in failure rate and egg reduction rates were detected between two and three doses of 10 mg/kg, given fortnightly in a trial of 81 participants (Rey *et al*. 1984). By contrast, there were fewer parasitological failures with the three dose regimen over the one dose regimen at the one month follow-up (RR=2.75, 95% CI: 1.29–5.85; n=93 participants) and the four-month follow-up (RR=1.52, 95%CI: 1.03–2.25; n=111 participants).

Different PZQ doses versus standard regimen (40 mg/kg x 1)

Ten trials compared the standard regimen of PZQ (single dose of 40 mg/kg) to various other doses (McMahon & Kolstrup 1979; Davis *et al*. 1981; Omer 1981; Oyediran *et al*. 1981; Rey *et al*. 1983; Kardaman *et al*. 1985; Wilkins & Moore 1987; Taylor *et al*. 1988; King *et al*. 1989, 2002). In terms of parasitological failure, there was no significant difference between the standard regimen and 2 x 20 mg/kg (4 trials), a single dose of 30 mg/kg (6 trials), and a single dose of 20 mg/kg (2 trials). Similar results were found at one, three and six months follow-up. Losses to follow-up were generally high, but these did not differ across treatment and control groups within a single trial. There was no significant heterogeneity between the trials, and background endemicity did not seem to play a role. Examining for a differential effect between heavy and moderate or light infections with 30 mg/kg versus standard 40 mg/kg, a subgroup analysis of one small trial (King *et al*. 1989) did not show any difference (n=116 participants). Five trials showed no apparent differences in egg reduction rate (geometric mean); all had greater than 95% reduction in both arms.

Artesunate

Thus far, only one randomised controlled trial conducted in Gabon in schoolchildren compared the effects of artesunate combined with PZQ to each individual drug given as monotherapy (Borrmann *et al*. 2001). Whilst the artesunate-PZQ combination resulted in a relatively higher egg reduction rate, it was not possible to identify an effect of artesunate, as no significant difference was observed in cure rates when compared to PZQ alone.

4.4 Methodological limitations

Lack of standardization and quality data for the assessment of efficacy and safety of antischistosomal drugs was reported previously for *S. mansoni* (Danso-Appiah & de Vlas 2002). In this Cochrane systematic review (Danso-Appiah *et al*. 2008), we identified a number of methodological limitations that raise issues with trial quality and

the potential for bias, outlined below. Some of the shortcomings have implications for the interpretation of trials in schistosomiasis and other tropical diseases (responses to methodological limitations summarised in Box 4.1).

Box 4.1 Responses to methodological limitations of trials included in a Cochrane review of drugs for treating urinary schistosomiasis (Danso-Appiah et al. 2008)

Design issues

1. There is the need for an unified study methodology in the design, collection and reporting of trials.
2. Trialists should be sensitized to the importance of proper sample size calculation to ensure that trials are sufficiently powered. High losses to follow-up in trials with small sample sizes further compromise the statistical power.
3. There is the need to clearly describe the randomisation procedure.
4. There is a need for standardized, quality-controlled diagnostic criteria within and between trials.
5. In high endemicity areas a follow-up time of 4 to 8 weeks is appropriate when investigating cure rates to avoid eggs released from dead worms and minimise the effect of re-infection.

Interpretation and reporting

6. Intensity of infection and egg reduction rate (ERR) should be reported in geometric mean, and intensity of infection should be based on egg count of only the positive cases and reported using the standard classification by the WHO (WHO, 2002).
7. Treatment outcomes need to be clearly defined and standardised across trials. Parasitological outcomes should be reported with; (1) level of edemicity, (2) diagnostic criteria, (3) dose used, (4) age of participants and (5) follow-up time.

1. *Some trials had no proper sample size calculation:* this suggests the authors may not have considered whether their study was sufficiently powered to answer the question being posed.
2. *Randomisation quality was not high:* only four out of 24 trials (17%) met quality standards for adequate concealment of allocation and described the methods used (for quality standards see Ju¨ni *et al*. (2001) and Higgins & reen (2008). Trials conducted in the early 1990s and earlier did not conceal allocation except one (Davis *et al*. 1981). Generation of allocation sequence was adequate in less than half of the trials included in our meta-analysis. For the others, the method used was unclear although all were reported as randomized controlled trials.
3. *Losses to follow-up were often high in some trials, and increased proportionally with the duration of follow-up:* 17 trials registered losses of <10% for short-term evaluations at one to three months, but losses reached up to 50% in some trials when follow-up time was longer than three months.

4. *Diagnostic criteria were varied, vague and not standardised:* among the trials included in our meta-analysis, the criteria for diagnosis varied greatly; some trials used three urine specimens on three consecutive days for microscopic examination, whilst others used a single specimen (Table 4.1). In some trials sampling criteria varied even between pre- and post-treatment using microscopy (e.g. three urine specimens for the pretreatment diagnosis but only one for post-treatment follow-up assessment) while other trials lacked any criteria for diagnosis.
5. *Classification of infection intensities lacked standardization:* Table 4.2 shows considerable variation in the classification of infection intensity cross trials. According to current WHO guidelines, infection intensity of *S. haematobium* is either light (1–49 eggs/10 ml of urine) or heavy (≥50 eggs/10 ml of urine) (WHO, 2002). In the trials included in our meta-analysis, however, light infections were variably classified as 1–5, 1–29, 1–99, 60–249 or even 250–500 eggs/10 ml of urine. Accordingly, moderate and heavy infections varied from one trial to another.
6. *Outcomes were reported in a variety of ways:* in our review we defined primary outcomes as (i) parasitological failure and (ii) egg reduction rate. However, these two measures were variably reported as cure rate, failure rate, cumulative failure rate or prevalence for parasitological failure, and as a median, arithmetic mean or geometric mean for egg reduction rate. Even the calculation of geometric mean varied; some investigators considered only the egg-positive individuals, whilst others included the negatives and introduced a correction factor of plus 1. The latter becomes problematic after treatment when most of the remaining infections are light, as it may overestimate egg count values.
7. *Timing of post-treatment assessments varied greatly:* the majority of trials evaluated cure and egg reduction rate within one to three months; however, some trials did so at three weeks or earlier, or only six or even 12 months post-treatment. Results from studies on urinary schistosomiasis assessing outcomes earlier than three weeks or beyond three months post-treatment should be considered with caution. The reasons are that the development of *S. haematobium* worms takes approximately two months (Ghandour 1978); shorter follow-up is confounded by eggs of killed worms still being excreted, longer follow-up by re-infections, particularly in highly endemic settings (N'Goran *et al*. 2001; Tchuem Tchuente' *et al*. 2004; Satayathum *et al*. 2006). Noteworthy, most of the trials in this review were conducted in high endemicity areas and there was no way in differentiating between re-infection and recrudescence.

Table 4.2 Classification of different S. haematobium infection intensities in clinical trials included in a Cochrane systematic review (Danso-Appiah *et al.* 2008), n.c. not classified

***S. haematobium* infection intensity (eggs/10 ml urine)**			**Reference**
Light	**Moderate**	**Heavy**	
60-249	250-499	≥500	Omer (1981)
250-500	501-1000	≥1000	McMahon (1983)
1-5	6-50	>50	Rey, Nouhou and Sellin, (1984)
1-29	30-99	100-500	Stephenson *et al.* (1985)
1-99	100-399	≥400	King *et al.* (1988)
<100	n.c.	≥100	Taylor, Murare and Manomano (1988)
1-29	30-99	100-499	Stephenson *et al.* (1989)
1-99	100-399	≥400	King *et al.* (1989)
1-99	100-399	≥400	King *et al.* (2002)
1-49	n.c.	≥50	WHO (2002)

4.5 Discussion

Public health implications

Despite the above-mentioned methodological limitations, the findings of our Cochrane systematic review have important public health implications. One of the most important findings is that both PZQ and metrifonate are efficacious and safe (Danso-Appiah *et al*. 2008). The failure rate with the recommended standard dose of PZQ (40 mg/kg) is 0-37%, whilst that of metrifonate (3 x 7.5-10 mg/kg given fortnightly) is 19-48% at one to three months follow-up. However, no trial included in our analysis directly compared the above-mentioned standard doses, therefore precluding any head-to-head assessment of the two treatments from currently available data.

Although the effects of PZQ against placebo are obvious, for some comparisons between regimens with both PZQ and metrifonate there was uncertainty around their effect estimates as shown by the wide 95% CIs. The small sample size in some of the trials may explain the levels of uncertainty. However, the magnitude of the effect is at times so dramatic that it is unlikely that methodological quality alone will have caused substantive biases to interfere with the marked effects and differences reported.

No difference was demonstrated with a single dose of 20 or 30 mg/kg of PZQ compared to the standard regimen (single oral dose of 40 mg/kg) in terms of all outcomes measured in this review. Given the current emphasis on controlling

morbidity in high-burden areas (WHO 2002), and morbidity, especially among school-aged children, being associated with the number of eggs in an individual, this finding suggests lower doses of PZQ may be effective in morbidity control. However, these results should be considered with caution as detection error can play a role, especially when the studies are few and sample sizes are small. While it is true that parasite load (with egg counts often used as a proxy measure) is an important factor in both morbidity for the individual patient and environmental contamination (WHO 2002), a sub-curative dose may unduly put the drug under selective pressure and favour parasite resistance (Doenhoff 1998; Doenhoff *et al*. 2008). Pharmacokinetic data of different doses of PZQ are few and old, and have been obtained in healthy volunteers rather than in schistosome-infected patients (Leopold *et al*. 1978). An exponential increase was found in the area under the curve (AUC) with the PZQ dose in the range of 5 to 50 mg/kg, with a six-fold increase from 20 to 50 mg/kg (Leopold *et al*. 1978). However, these data do not come from infected patients, and hence cannot be extrapolated so easily. This calls for well designed trials incorporating also pharmacokinetic assessment, possibly with sparse sampling and population kinetic assessment. These trials should also control for food intake, as the bioavailability of PZQ depends upon taking it with food and the type of food matters (Mandour *et al*. 1990; Castro *et al*. 2000).

The rationale behind the widely spaced dosing intervals of metrifonate treatment derives from its long-lasting effect on red blood cells and plasma cholinesterases (Plestina *et al*. 1972). However, the clinical significance of this effect and why side effects disappear during the first 12–24 hours whereas the recovery of the enzymes takes more than 4-6 weeks is not known (Plestina *et al*. 1972). Safety studies have shown no serious adverse events in patients treated with 5-10 mg/kg metrifonate daily for 6-12 days (Snellen 1981), and various reviews of the toxicology and pharmacology of metrifonate during its extensive use for urinary schistosomiasis in the 1970s concluded that it had very few adverse events (Holmstedt *et al*. 1978; Feldmeier & Doehring 1987; Cioli *et al*. 1995). Also, metrifonate is currently used in Alzheimer's disease in extended regimens, and a systematic review has concluded that overall tolerability is good with only mild to moderate adverse events (Lo´pez-Arrieta & Schneider 2006). In the current review, although drug safety was generally poorly reported and assessed in few trials, no trial recorded a serious adverse event, and no significant differences in the number and type of adverse events between metrifonate and PZQ were recorded, except for abdominal pain that was more frequent after metrifonate. Optimizing metrifonate treatment may provide a means of easing drug pressure exerted on schistosomes by the wide deployment of PZQ.

Immature schistosomes are less sensitive to PZQ than adult worms (Sabah *et al*. 1986), which has raised concern about controlling schistosomiasis effectively with this drug. Artemisinin derivatives proved to be effective against immature schistosomes in laboratory studies (Utzinger *et al*. 2003, 2007). However, this review shows that artesunate was not effective against *S. haematobium* infections (though evidence was derived from a single trial (Borrmann *et al*. 2001)), and combining artesunate and 40 mg/kg PZQ did not improve efficacy over PZQ alone. In two non-randomised trials involving artesunate alone, results were relatively better (De Clercq *et al*. 2002; Inyang-Etoh *et al*. 2004). The latter findings were confirmed in a recent trial; artesunate alone (4 mg/kg) resulted in a cure rate of 70.5%, whereas an artesunate-PZQ combination obtained a cure rate of 88.6% (Inyang-Etoh et al. 2009). Finally, a recent trial in children under six years of age who were co-infected with *Plasmodium falciparum* and *S. haematobium* and who were treated with two different artemisinin-based combinations for malaria therapy showed good effects on *S. haematobium*. This trial, however, could not be included in the current analysis because there was no control group (Boulanger *et al*. 2007).

The need for good trial methods

The validity of randomized controlled trials rests in part on adequate allocation concealment and minimal losses to follow-up, and weaknesses in both these aspects were found in the trials included in the current meta-analysis (Table 4.1). Without adequate allocation concealment properly developed random allocation sequences can be subverted (Schulz & Grimes 2002). A likely explanation for only four trials (17%) included in our final analyses adequately concealing allocation is that this had not been identified as a particularly relevant issue at the time the trials were conducted (20-30 years ago). Even after the publication of the CONSORT statement (Begg *et al*. 1996) and despite continued educational efforts, the quality of reporting of randomized controlled trials still needs improvement (Altman *et al*. 2001; Moher *et al*. 2001).

The effect of losing patients during follow-up on randomisation is crucial as this relates to the internal validity and the power of the trial. In our systematic review we could not do a sensitivity analysis to evaluate the effect of loss to follow-up because data were not sufficient. We encourage trialists to take particular note of this issue and ensure that losses are minimised and power is preserved in future trials. Also, we welcome debate on the most appropriate timing of follow-up in evaluating drug trials of both urinary and intestinal schistosomiasis. The biology of schistosomes suggests that treatment effects with antischistosomal drugs on parasitological parameters should be evaluated during a window of four to eight weeks post-

treatment to avoid detecting the tail of eggs released from dead worms on one side, and re-infections on the other side. A first attempt has been made to evaluate this for intestinal schistosomiasis due to *S. mansoni*, and the authors concluded that three weeks after PZQ administration is an appropriate timing for drug efficacy evaluation (Scherrer *et al*. 2009).

Safety is generally overlooked and when data are available they are poorly reported. It is important that trialists realise the importance of adequately documenting and reporting on tolerability.

Diagnostic concerns

The quality of diagnosis can influence the observed cure rates as clearly shown for both *S. mansoni* (de Vlas & Gryseels 1992; Booth *et al*. 2003) and *S. haematobium* (N'Goran *et al*. 2003). Sensitivity will affect in particular the detection of light infections during follow-up. We found considerable variation in diagnostic criteria not only between, but also within trials, also with regard to infection intensity. This may be explained by the fact that the WHO classification as light (1–49 eggs/10 ml urine) and heavy infection intensity (≥50 eggs/10 ml urine) was endorsed only recently (WHO 2002) and was not in use when the trials summarized here. Because of the different thresholds used for infection intensity, it was not possible to combine and analyse the data according to heavy infections, which is relevant to morbidity control.

Study population issues

The age of participants enrolled in randomized controlled trials may also influence results. Here, 22 trials out of 24 recruited school-aged children. Hence the overall effect estimates as reported in this review may be lower than studies including all-age subjects, as adults usually show lower infection intensities than school-aged children and, conversely, higher treatment efficacies. This issue has been documented for *S. mansoni* (Raso *et al.* 2004), and it is conceivable that the same holds for *S. haematobium*. It should also be noted that restricting treatment to school-aged children leaves untreated adults and pre-school children still excreting eggs to maintain transmission, if indeed transmission is a function of egg output. This brings us to two important sets of considerations. First, data should be reported separately for children and adults before, if necessary, pooling the data to assess overall effects. Second, the purpose of studies depends on the target population. Studies in children receiving antischistosomal treatment are more apt to assess the 'true' efficacy of the drug because drugs such as PZQ have an immune response-dependent component (Doenhoff *et al*. 1987), which is more active in adults, while whole-population studies

are more suited to assess the programmatic effectiveness and effects of control interventions.

4.6 Implications for policy

Both PZQ and metrifonate are effective and safe for treating urinary schistosomiasis. Our systematic review and that of Lo´pez-Arrieta & Schneider (2006) indicate that metrifonate is well tolerated. Although in schistosomiasis control metrifonate has operational drawbacks, notably multiple administrations, which make it less convenient for large scale morbidity control programmes than a single dose of PZQ, the two drugs have similar efficacy profiles. Furthermore, considering that schistosomes are under intense and growing drug pressure by PZQ and the inherent vulnerability of schistosomiasis control to parasite resistance, we suggest metrifonate should be reconsidered for the treatment of urinary schistosomiasis, to ease the drug pressure on PZQ. This implies continued availability (production and distribution) of the drug. It is also important to have an alternative drug for treating urinary schistosomiasis should PZQ resistance emerge.

Most of the trials contributing to this review were conducted more than a decade ago, and entail a series of methodological limitations. The new schistosomiasis trials must be conducted to contemporary standards of clinical research paying particular attention to quality issues we have raised, and adopt commonly agreed criteria.

Our findings point to new approaches worth being explored in well-designed trials such as: (1) reassessing appropriate dosing schedules for metrifonate, including compliance and feasibility in control programmes; (2) comparing standard metrifonate (3 x 7.5–10 mg/kg given fortnightly) and PZQ (1 x 40 mg/kg) doses; (3) evaluating artemisinin-based regimens and combination treatments where appropriate (areas where malaria and schistosomiasis are not co-endemic); and (4) obtaining pharmacokinetic/pharmacodynamic correlates for PZQ.

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Chapter 5

Determinants of health seeking behaviour for *schistosomiasis*-related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana

Danso-Appiah A, De Vlas SJ, Bosompem KM, Habbema JDF. Determinants of health seeking behaviour for schistosomiasis-related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana. *Tropical Medicine & International Health* 2004;9:784-94.

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5.1 Abstract

Morbidity control of schistosomiasis through integration within existing health care delivery systems is considered a potentially sustainable and cost-effective approach. We conducted a questionnaire-based field study in a Ghanaian village endemic for both urinary and intestinal schistosomiasis to determine whether infected individuals self-reported to health centres or clinics and to identify factors that influenced their decision to seek health care. A total of 317 subjects were interviewed about having signs and symptoms suggestive of schistosomiasis: blood in urine, painful urination, blood in stool/bloody diarrhoea, abdominal pain, diarrhoea, swollen abdomen and fatigue within 1 month of the day of the interview. Fever (for malaria) was included as a disease of high debility for comparison. Around 70% with blood in urine or painful urination did not seek health care, whilst diarrhoea, blood in stool, abdominal pain and fever usually led to action (mainly self-medication, with allopathic drugs being used four to five times more often than herbal treatment). On average 20% of schistosomiasis-related signs and symptoms were reported to health facilities either as the first option or second and third alternative by some of those that self-medicated. A few of those who visited a clinic or health centre as first option still self-medicated afterwards. Children under 10 years and adults were more likely to seek health care than teenagers. Also, females were more likely to visit a health facility than males of the same age groups. Socio-economic status and duration of symptoms did not appear to affect health-seeking behaviour. 'Do not have the money' (43%) and 'Not serious enough' (41%) were the commonest reasons for not visiting a clinic, reported more frequently by lower and higher socio-economic classes, respectively, for both urinary or intestinal schistosomiasis. The regular health service shows some potential in passive control of schistosomiasis as some, but far too few, people visit a health facility as first or second option.

5.2 Introduction

Schistosomiasis affects mostly children, farmers and women who depend on daily water contact for domestic and occupational activities. The disease is especially important in poor, rural areas, where attempts to alleviate poverty also promote small-to-large scale water-related development projects that may increase transmission.The effects of the disease are varied. Urinary schistosomiasis (caused by *Schistosoma haematobium*) leads to blood in urine (haematuria) and painful urination (dysuria) as early symptoms whilst secondary bacterial infection, calcification of the bladder wall, bladder stones, bladder carcinoma, hydronephrosis and kidney failure are late stage complications. Intestinal schistosomiasis (caused by *S. mansoni*) gives rise to blood in stool or (bloody) diarrhoea and abdominal pain. Also, inflammatory reactions in the liver lead to hepato-splenomegaly. Later-stage lesions become fibrotic and progressively occlude the portal system, leading to portal hypertension that may precipitate haematemesis from ruptured oesophageal varices. Female and male genital schistosomiasis reduces fertility and may promote the spread of HIV/AIDS (Leutscher *et al.* 2000; Poggensee & Feldmeier 2001). Furthermore, the overall vitality and academic performance of children is affected (Nokes *et al.* 1999).

Until recently, control of schistosomiasis was largely based on vertical programmes (Gryseels *et al.* 1991; el Malatawy *et al.* 1992; Barakat *et al.* 1995), with separate budgeting from regular health services supported by donor organizations. The 'vertical' concept aims at reducing prevalence of the infection, and thereby morbidity, through active case finding. Within this approach, treatment of infected individuals or target groups with the standard dose of 40 mg praziquantel/kg body weight is applied in many endemic countries (WHO 1985). Although reinfection occurs, particularly in children, pathology is resolved or at least its development is delayed (Mohamed-Ali *et al.* 1991; Doehring-Schwerdtfeger *et al.* 1992; WHO 1993; Wagatsuma *et al.* 1999). Through the vertical approach, treatment is targeted at school children in many endemic areas (Engels *et al.* 1994; The Partnership for Child Development 1999). Nevertheless, the vertical approach has not been sustainable because of high cost and rapid reinfection (Kumar & Gryseels 1994). The inability to sustain schistosomiasis control has prompted many endemic countries to consider integration of control activities within the regular health services, 'the horizontal approach', as a more viable alternative (Tanner & Degremont 1986; WHO 1993). This approach aims at providing treatment to those that self-report to health facilities with schistosomiasis-related signs and symptoms. The assumption here is that, if signs and symptoms are recognized early enough by the patients themselves, most severe forms of pathology that develop later can be prevented.

In Ghana, schistosomiasis assumed major importance as a public health problem in the early 1960s following construction of the Akosombo dam (Paperna 1970). The resulting lake Volta, 8730 km^2, created a vast area suitable for the breeding of schistosome host snails. Before the construction of the dam, prevalence of *S. haematobium* was 5–10%; it rose to >90% in most communities along Volta lake, raising serious public concern (Lavoipierre 1973; Scott *et al.* 1982). In spite of international control efforts for over three decades, urinary schistosomiasis remains widespread (Scott *et al.* 1982; Aryeetey *et al.* 2000). The situation was worsened by rapid increase in the prevalence of intestinal schistosomiasis at the lower Volta (Odei 1983; Wen & Chu 1984). *Schistosoma mansoni*, until recently a rare species in Ghana (Rambajan 1994), now is common in the northern parts of the country (Amankwa *et al.* 1994).Intensive control efforts have been made (Chu 1978;Aryeetey *et al.* 2000) including mass chemotherapy in primary schools initiated in the early 1990s under The Partnership for Child Development (1999) Programme. However, as in most endemic countries with economic constraints, sustainability of large-scale vertical control programmes has not been achieved.

Currently, Ghana is restructuring its health care delivery system to strengthen the peripheral health facilities. In the decentralized health system, integrating parasitosis control into the regular health services is essential. However, being a chronic illness with mostly mild-to-moderate debilitation, the seriousness of schistosomiasis at the community level can be underestimated (Tanner *et al.* 1986; Gazzinelli *et al.* 1998) and the tendency for individuals to self-report at health centres can be low.

Studies on health-seeking behaviour in schistosomiasis have focused mainly on knowledge, attitude and practices (KAP) in relation to the status of the infection as measured by prevalence or morbidity (Kloos 1995; Gazzinelli *et al.* 1998; Aryeetey *et al.* 1999; Curtale *et al.* 1999). There is hardly any study that has evaluated the determinants of passive case reporting to existing health care delivery systems. It is well noted that, whilst such epidemiological studies are sufficient to establish prevalence figures and distribution of knowledge and practices, they do not necessarily infer any causal associations or consequence on particular actions taken. Various factors emanating from the household, community and national levels, or even introduction of internationally driven policies such as the cost recovery system directly or indirectly influence health-seeking behaviour. Understanding peoples' health-seeking behaviour and factors influencing the decision to self-report with schistosomiasis-related signs and symptoms is, therefore, highly relevant for health planners and policy-makers towards integration of parasitic diseases control within the regular health services.

The main objective of this study was to investigate health care-seeking behaviour of patients with signs and symptoms suggestive of schistosomiasis in an endemic population in Ghana and describe the decision-making process for obtaining health care. Also, the determinants of case reporting to the existing (regular) health care delivery system, which are essential to the success of integrated control of the disease, were investigated.

5.3 Materials and methods

Study area and population

A questionnaire-based field study was carried out in Kokoetsekope, a village of 380 inhabitants located in the Greater Accra Region of Ghana. It is one of the clusters of villages situated along the Densu lake formed as a result of damming the Densu river. The lake is the main source of water supply to Accra and the surrounding towns. The village is endemic for both urinary and intestinal schistosomiasis. In a preliminary pilot survey by the Noguchi Memorial Institute for Medical Research (NMIMR) in the same population, prevalence rates of *S. haematobium* and *S. mansoni* were found to be 70% and 78%, respectively. The general vegetation is the coastal savannah type with short grass and scattered bushes. Along the shores of the lake are aquatic plants, which harbour the schistosome host snails (*Bulinus truncatus rohlfsi* and *Biomphalaria pfeifferi*), making the lake the main source of infection. The inhabitants fetch untreated water from the Densu lake for drinking, bathing and domestic activities, whilst others, particularly children, swim in it.

Kokoetsekope is inhabited mostly by migrant workers and their families from fishing communities in the Volta Region of Ghana. It is a young population: 44% are children under 15 and 3% adults over 60. There was no difference in number between males and females. The general educational status of individuals aged 15 years and above was low; 24% never attended school and 60% had only elementary education, mostly incomplete. Adult women >15 years of age engaged in petty trading, while most men worked as fishermen, farmers or labourers. Multiple occupations were common among both genders.

The health facilities used by the people are located in Kasoa, a nearby commercial town about 2 km away. There were a total of 13 health care facilities where the inhabitants of Kokoetsekope reported to have visited for medical care. Two were health centres and 11 private clinics. Also, there was a chemical shop in Kokoetsekope from which individuals obtained drugs. Both health centres were level B type of the primary health care system, and mostly without laboratory facilities. Of the 11 clinics,

four provided both maternity and clinical care and were headed by midwives, two combined clinical and herbal treatment and the remaining five were regular clinics headed by qualified medical doctors or nurses. The health centres were government owned and manned by medical assistants. In these health care facilities treatment for schistosomiasis was usually based on signs and symptoms. The system of payment for health care delivery was *cash and carry* (out of pocket payment) where a patient was required to make full payment for consultation and laboratory investigations before treatment was provided. Within the cash and carry system, mostly essential drugs are kept in the health facilities. Thus, patients attending these health facilities obtained drugs prescribed to them from private pharmacies.

Data collection

The interviews took place between July and September 2000. Opinion leaders and community members were first informed about the study in a *durbar* and their consent sought. Subjects were assured about confidentiality of information obtained from them. Thereafter, a detailed plan of the study and its objectives were submitted to the Ethical Committee of Ghana Ministry of Health for approval, which was granted in August 1999. The study village was divided into six sectors based on topographical landmarks and proximity to the lake. House numbers were assigned to all the houses and each inhabitant was registered according to household. Each subject was assigned an identification code defining the village, location of house and serial number.

A pretested questionnaire developed in English was translated into the local language (Twi) and administered to all the inhabitants. The questionnaire was made up of a demographic section including name, age, sex and house number of subjects; decision-making indicators such as who requests health care, who provides money for health care; socio-economic indicators such as level of education, occupation and property owned; indicators of schistosomiasis-related signs and symptoms such as duration and severity; and action taken. The signs and symptoms covered by the questionnaire were: blood in urine and painful urination (for urinary schistosomiasis); blood in stool/bloody diarrhoea, diarrhoea, abdominal pain and swollen abdomen (for intestinal schistosomiasis); and fatigue (non-specific) an indication of anaemia, which could be the result of urinary and/or intestinal schistosomiasis. It should be noted that the signs and symptoms covered here are only suggestive of, but not necessarily, because of schistosomiasis. Fever (for malaria) was added as a disease of high debility for comparison. Questions about signs and symptoms were asked in a random order. Reported action taken could include multiple activities (e.g. first self-medication and then visiting a clinic). Individuals with reported signs or symptoms

who did not visit a health facility (clinic or health centre) were asked to give a reason. Respondents were asked about causes of blood in urine and bloody diarrhoea.

All registered individuals were interviewed. Parents or guardians answered for small children under 6 years. Potential respondents for individuals who could not answer for themselves were preferentially ranked as follows: mother, father, guardian (aunt, uncle or other close relatives). To minimize variability, the questionnaire, which took an average of 20 min, was administered by two trained interviewers. The socio-economic status of individuals was assigned by using the status of the household to which they belong. Three possessions (car, fridge and television) were selected as indicators of relatively high socio-economic status of a household. Any household owning one or more of these was considered as being in the relatively high category.

Also, we interviewed five health care facilities and four chemical shops serving Kokoetsekope about availability of praziquantel as well as prescription and treatment practices for a selection of schistosomiasis-related symptoms (blood in urine, painful urination, blood in stool and diarrhoea) with a modified version of a questionnaire that was used in other parts of Ghana (Van der Werf *et al.* 2003). Patients who visited a health facility or chemist were asked about their knowledge about what was provided or prescribed to them in three focused group discussions. Those who used traditional self-medication were asked about the kind of medicines taken.

5.4 Results

Table 5.1 summarizes data on decision-making process for seeking health care. The majority of adults responded to the interview themselves. Mothers and fathers were the key decision-makers about health care for dependent children. Other family members who made decisions for younger children were guardian (uncle and aunt), sisters and brothers. Mothers usually requested health care for children under 10 and accompanied them to the health care facility, while fathers often provided financial support. The roles of mothers declined with increasing age of the child, whilst that of fathers increased. Some teenagers started paying for their health care as early as at age 14, particularly those not attending school. Most adults over 20 reported paying for health care services themselves, although some, mostly students and a few married women, were funded by parents and husbands. A few of the married couples accompanied either partner to a clinic/health centre. About 68% of those who had visited health facilities indicated that they usually spent half a day to obtain health care (data not shown).

Table 5.1 Factors influencing decision to seek health care with schistosomiasis-related signs and symptoms among inhabitants of Kokoetsekope

Variable	Respondent (%)	Request for care (%)	Financial provider (%)	Companion* (%)
Age 0-4 years (n = 51)				
Self	0.0	0.0	0.0	0.0
Mother	78.4	86.3	31.4	86.3
Father	5.9	9.8	56.9	9.8
Other	15.7	3.9	11.8	4.0
Age 5-9 years (n = 47)				
Self	31.9	10.6	0.0	0.0
Mother	34.0	51.1	36.2	63.8
Father	14.9	34.0	59.6	31.9
Other	19.2	4.3	4.3	4.3
Age 10-14 years (n = 40)				
Self	82.5	32.5	0.0	2.5
Mother	5.0	35.0	37.5	55.0
Father	5.0	22.5	47.5	22.5
Other	7.5	10.0	15.0	20.0
Age 15-19 years (n = 30)				
Self	96.7	70.0	13.3	30.0
Mother	0.0	10.0	26.7	40.0
Father	3.3	16.7	46.7	23.3
Other	0.0	3.3	13.4	6.7
Age 20+ years (n = 149)				
Self	98.7	97.3	59.7	84.6
Mother	0.0	0.0	2.0	1.3
Father	0.0	2.7	7.4	2.0
Other	1.3	0.0	30.9	12.1†

* Companion to clinic or health centre; in case of self, the individual was not accompanied.

† In most cases, the husband/wife.

Other = guardian, uncle, aunt, brother and sister.

Using a 1-month recall period (Figure 5.1), there were 64 reported cases of blood in urine (20%), 34 (11%) of painful urination, 73 (23%) of diarrhoea, 82 (26%) of blood in stool, 19 (6%) of swollen abdomen, 98 (31%) of abdominal pain, 93 (29%) of fatigue and 146 (46%) of fever. For diarrhoea, abdominal pain and fever, the number of cases tripled by including reported episodes that terminated in the month before interview. Figure 5.2a confirms that these symptoms showed acute patterns and rarely persisted beyond 1 month. On the contrary, more than 75% of subjects with blood in urine and those with painful urination reported persistent signs and symptoms for 1 year or longer. Similarly, blood in stool (60%) and swollen abdomen (50%) showed characteristic chronicity. Swollen abdomen and diarrhoea were typically associated with children under 10, whereas blood in urine and painful urination were reported by 38% of teenage boys and 2.8% of girls (data not shown). There were no gender differences for fever, abdominal pain and blood in stool. Fatigue was reported mainly by adults, particularly women. As shown in Figure 5.2b, 60–70% of subjects with painful urination, diarrhoea and fever considered these signs and symptoms as severe or moderate, whereas this was only 30–40% for blood in stool and swollen abdomen (Figure 5.2b). Swollen abdomen and diarrhoea were typically associated with children under 10, whereas blood in urine and painful urination were reported by 38% of teenage boys and 2.8% of girls (data not shown). There were no gender differences for fever, abdominal pain and blood in stool. Fatigue was reported mainly by adults, particularly women. As shown in Figure 5.2b, 60–70% of subjects with painful urination, diarrhoea and fever considered these signs and symptoms as severe or moderate, whereas this was only 30–40% for blood in stool and swollen abdomen (Figure 5.2b).

People reacted to signs and symptoms by doing nothing, self-medicating or visiting a health facility (Figure 5.3a). Most subjects with blood in urine and painful urination did not take any action, whereas >90% of those with fever did. Diarrhoea, blood in stool and abdominal pain usually led to action, mostly self-medication. Allopathic medication was used four to five times more often than herbal medicine. On average, 20% of schistosomiasis-related signs and symptoms were said to have been reported to health facilities as first option with some of those that self-medicated eventually visiting a clinic or health centre as a second or third alternative (Figure 5.3b). The results showed that some of those, especially with blood in stool, swollen abdomen and fever who visited a health facility as first option, still self-medicated afterwards. This practice was rare for diarrhoea, blood in urine and abdominal pain. Also, self-medication as first option followed up by visiting a health facility was regularly practised for fever (Figure 5.3b).

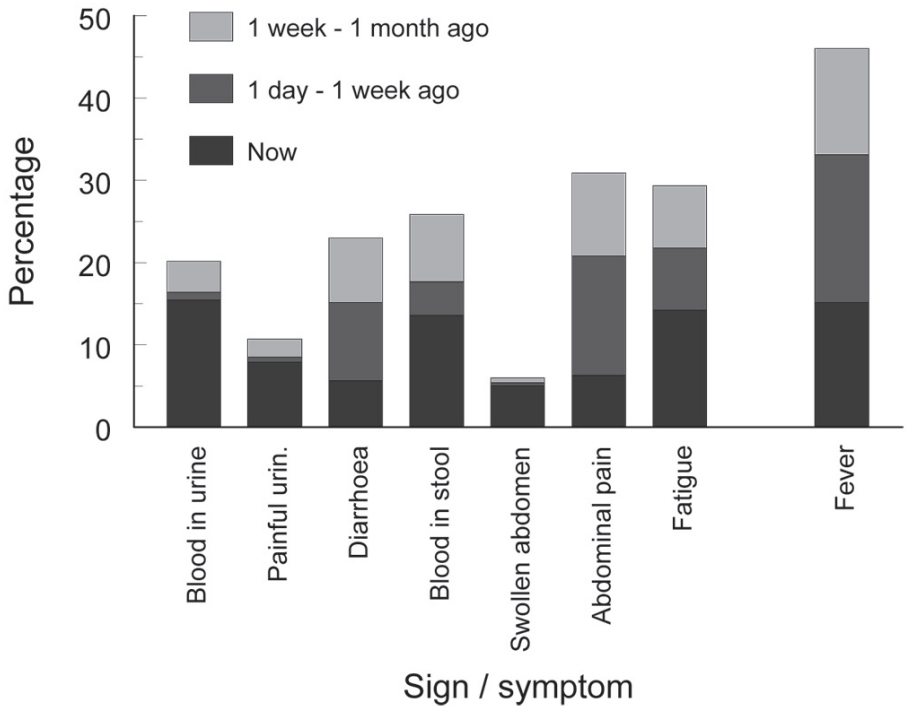

Figure 5.1 Reported presence of schistosomiasis-related signs and symptoms grouped into three recall periods among 317 interviewed inhabitants of Kokoetsekope (Ghana). Fever (for malaria) has been selected as a disease of high debility for comparison.

Children under 10 years of age and females were much more likely to visit health facilities as first option than teenagers (Table 5.2). For actions other than visiting a clinic/ health centre, no clear differences were observed except for male teenagers, who also showed a relatively low tendency here (Table 5.2). Similar analyses revealed that perceived severity of schistosomiasis-related signs and symptoms rarely increased health care seeking, and duration of signs and symptoms and socio-economic status of individuals did neither (data not shown).

Several reasons were given for not reporting to a clinic or health centre with signs and symptoms (Table 5.3). Of 460 responses given, 'Do not have the money' (43%) and 'Not serious enough' (41%) were most often mentioned. 'Do not have the money' was reported by 53% of individuals from the low socio-economic group, whereas this was 33% for the high social class. On the contrary, 'Not serious enough' was reported by 38% of the low and 54% of the high classes, respectively. All reported reasons were grouped into four categories: 'No money' (46.5%), 'Not serious enough'

(44.2%), 'Negative attitude towards health care' (4.5%) and 'Positive attitude towards self-medication' (4.8%). Answers in response to the different signs and symptoms did not show any clear pattern (Figure 5.4).

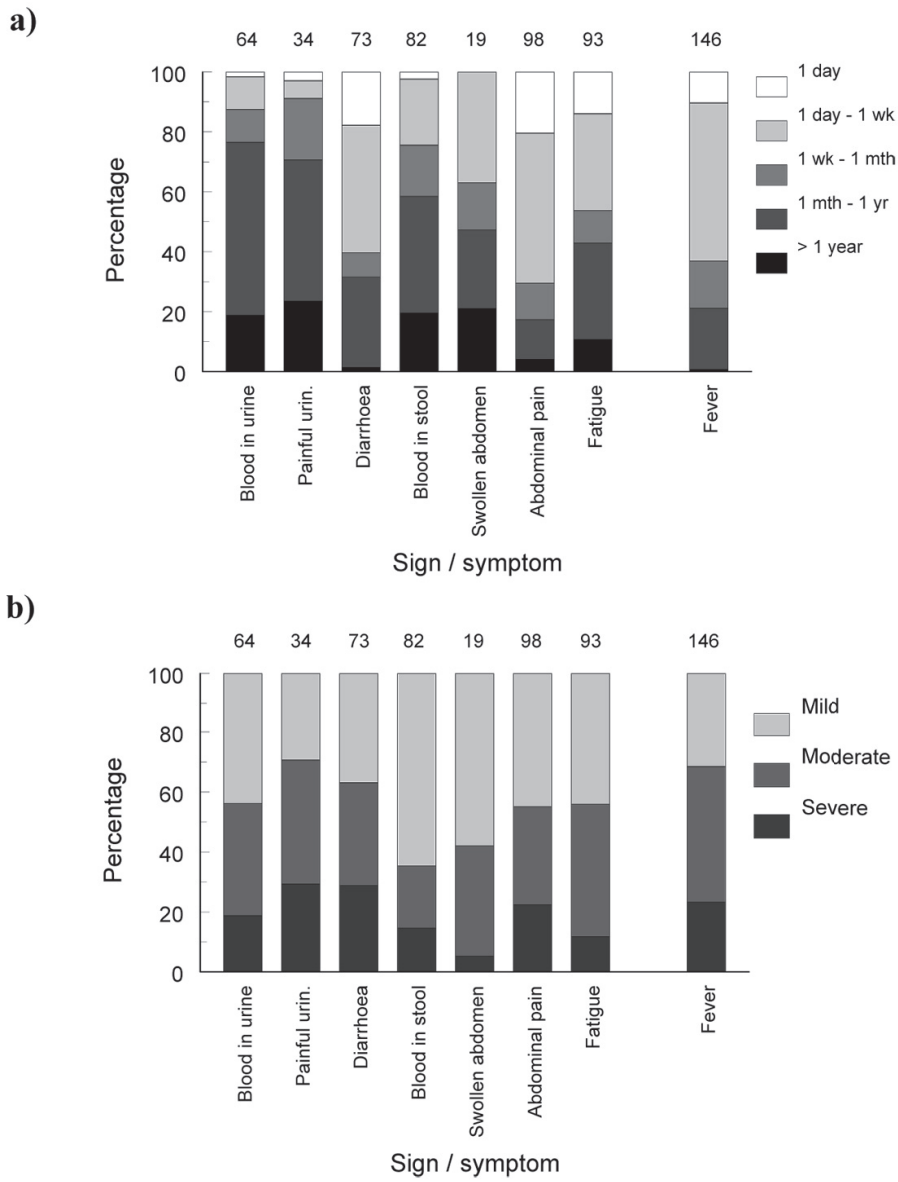

Figure 5.2 Reported duration with which individuals in Kokoetsekope have lived with their signs and symptoms (a) and their opinions about severity of schistosomiasis-related signs and symptoms (b). A debilitating sign, fever, (for malaria) has been selected for comparison.

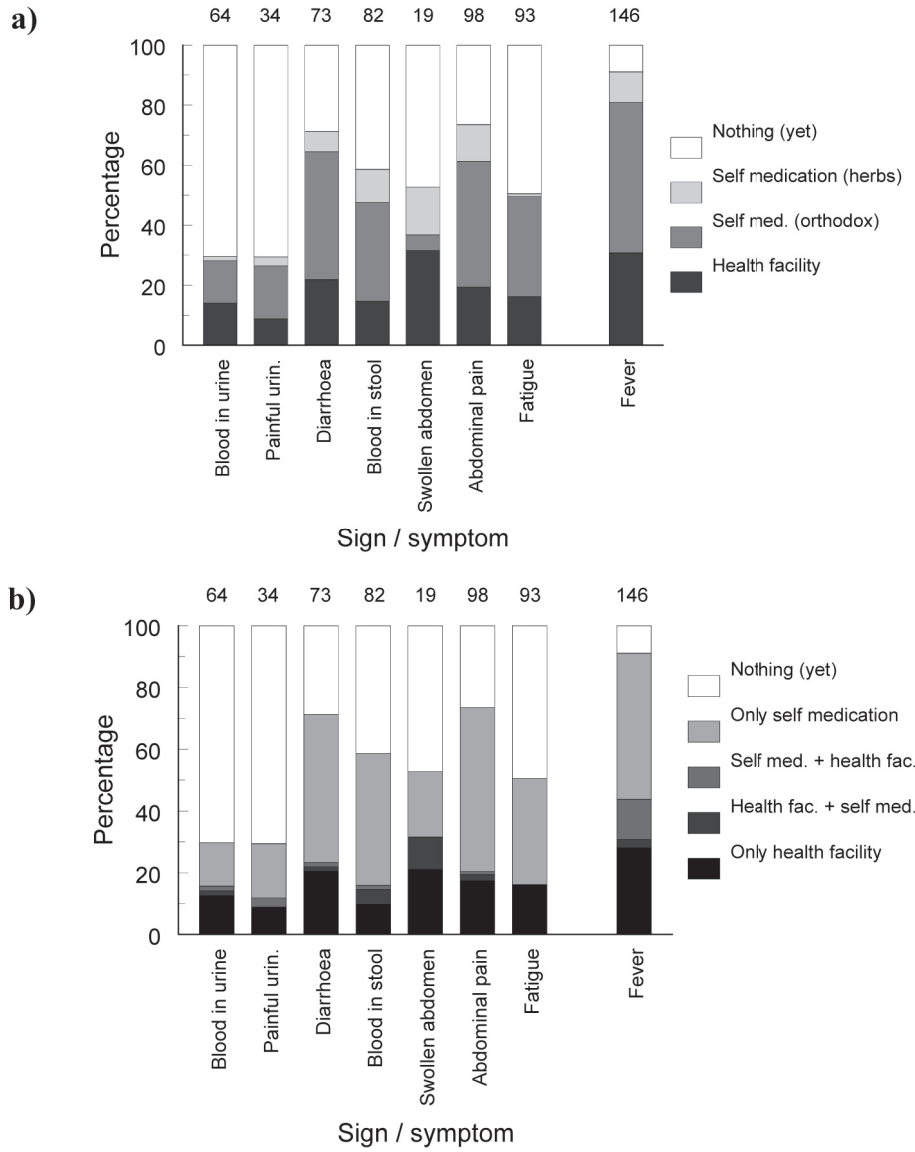

Figure 5.3 Reported action taken about schistosomiasis-related signs and symptoms (a) first action only and (b) first and second actions (first action followed by second). The values on top of the bars represent the total number of cases based on 1 month recall period. 'Health facility' indicates a hospital, clinic or health centre

Table 5.2 Reported actions taken in response to schistosomiasis-related signs and symptoms

	Child (0–9 years)		Teenager (10–19 years)		Adult (20+ years)		All
	Female	Male	Female	Male	Female	Male	
Number of cases*							
Urinary	10	15	10	34	6	23	98
Intestinal	36	46	24	35	46	66	253
Fever	23	22	18	19	35	29	146
Visiting a health facility as first action (% of number of cases)							
Urinary	20	13	10	6	33	17	13
Intestinal	36	17	17	6	13	21	19
Fever	48	27	28	37	26	24	31
Other action (% of number of cases)							
Urinary	20	27	10	6	0	30	16
Intestinal	44	46	50	31	65	53	49
Fever	52	64	56	47	63	72	60

*Urinary signs and symptoms included blood in urineand painful urination. Intestinal signs and symptoms included diarrhoea, blood in stool and abdominal pain. Fever (for malaria) was included for comparison. Some individuals reported multiple signs and symptoms, thus were represented more than once.

Regarding the population's knowledge about symptoms, about half (43%) of those who responded to the interview themselves reported that the lake was the cause of blood in urine, but only 7% specifically related blood in urine to schistosomiasis (or bilharzia). Only 7% associated bloody diarrhoea with the lake and nobody mentioned schistosomiasis (or bilharzia).

Only one health facility and none of the chemical shops stocked praziquantel. However, chloroquine (for treating malaria) was available in all health facilities and chemical shops. Over 90% of patients did not know what was prescribed or provided to them at the health facilities and chemical shops except for oral rehydration salt (ORS) and chloroquine. Knowledge, prescription and treatment practices of health care providers were associated with the level of training received. Cases of blood in urine were most likely to receive a prescription of praziquantel (four of the five health care facilities interviewed) compared with blood in stool and painful urination (both one of five) and diarrhoea (none). Cases of diarrhoea would usually receive ORS and antibiotics. The majority of those who self-medicated or visited chemical shops for treatment were given flagyl (Metrinidazole) and antibiotics. One of four chemical

shops would have provided praziquantel for blood in urine, if it were available. Still, many did not have any idea about the kind of drugs provided or prescribed to them. No known traditional medicine was used for treating schistosomiasis-related symptoms except for blood in stool where some subjects used ginger plus pepper.

Table 5.3 Reported reasons (n = 460) for not attending a health facility (clinic or health centre) with schistosomiasis-related signs and symptoms

Reason	Number of responses	%
Financial difficulties		
Do not have the money	200	43.5
Too expensive	14	3.0
Seriousness of symptoms		
Not serious enough	187	40.6
Too busy	9	2.0
Waiting for sometime	4	0.9
Too far away*	3	0.7
Negative attitude towards health care		
Drugs do not help	20	4.3
No drugs	1	0.2
Positive attitude towards self-medication		
Self-medication effective	10	2.2
Waiting for drug peddler	6	1.3
Waiting for effect of self-medication	4	0.9
Used previous drugs	1	0.2
Used old prescription to buy drugs	1	0.2

* The distance to the furthest target health facility is 2 km.

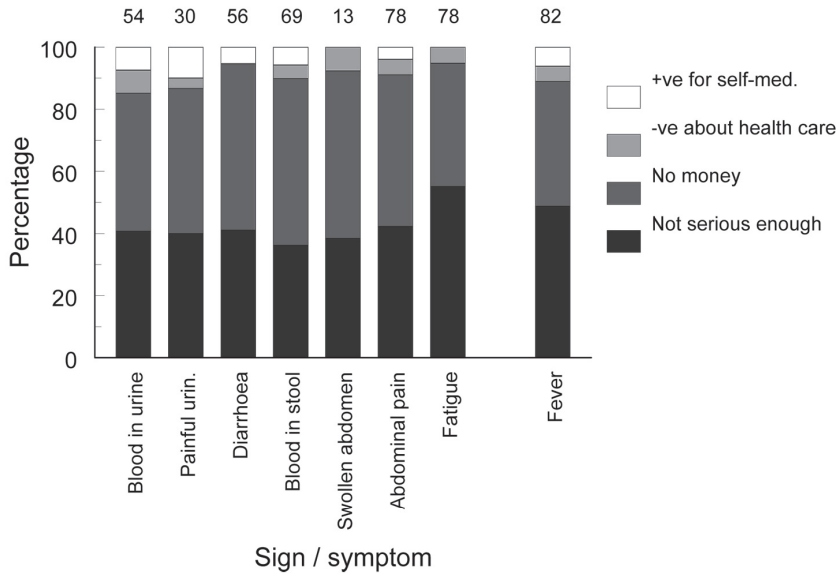

Figure 5.4 Reported reasons for not going to a health facility (clinic or health centre) for four categories of answers given. The values on top of the bars represent the number of cases (1 month recall) that did not visit a health facility with their sign or symptom.

5.5 Discussion

Many studies have investigated the effect of KAP on seeking health care for infectious diseases (Ruebush *et al.* 1995; Sodemann *et al.* 1997; Soucat *et al.* 1997; Jaramillo 1998; Ahmed *et al.* 2000; Geissler *et al.* 2000; Oberlander & Elverdan 2000; Thorson *et al.* 2000; Needham *et al.* 2001). Nevertheless, the impact of knowledge and attitudes on regular health care use has not been widely studied. KAP studies on schistosomiasis (Kloos 1995; Gazzinelli *et al.* 1998; Aryeetey *et al.* 1999; Curtale *et al.* 1999) established prevalence figures and distribution of knowledge and practices, but did not show consequences on particular actions taken. Our aim was to determine these factors and their influence on the use of health facilities in a schistosomiasis endemic community.

Keller *et al.* (1997) compared 1-week recall for measurement of acute properties with the standard (1-month recall) and found that 1-week recall yielded high-quality

data. Also, Schulpen and Swinkels (1980) showed that 60% of subjects in Kenya under-reported self-medication of common illnesses using a recall period of 2 weeks. Given the recall of one month for this study, we anticipated under-reporting by subjects with mild schistosomiasis-related signs and symptoms. Strikingly, subjects who had never experienced symptoms, those who had, and those with ongoing symptoms did not show differences in the reported tendency to visit health facilities or other health-seeking practices. This justified the inclusion of cases up to 1 month in our analysis. In a study of non-fatal injuries in Ghana, Mock *et al.* (1999) reported that 1 month recall was appropriate. The findings of this work therefore suggest that in schistosomiasis morbidity studies 1 month recall period is suitable, although there is a need for further studies to ascertain the applicability of this time frame for both the urinary and intestinal diseases.

Except for haematuria, many of the signs/symptoms are neither specific nor sensitive for the diagnosis of schistosomiasis. Although no parasitological examination was performed to link symptoms with specific disease, the number of individuals reporting symptoms that have schistosome infection was undoubtedly high as we found 78% infected with *S. mansoni* and 70% with *S. haematobium* in a random sample of the population. Still, it is not certain that a symptom suggestive of schistosomiasis was the result of schistosome infection. In particular, diarrhoea and abdominal pain could very well have resulted from causes other than *S. mansoni* infection. If so, our findings for such cases may still be informative, as it is not very likely that health-seeking behaviour depends much on the cause of a particular symptom. For those who did take action for blood in urine or blood in stool, it is certain that fear of schistosomiasis was not the reason, as hardly anybody linked these symptoms to schistosomiasis. This is in contrast to fever, a term loosely used to refer to clinical malaria in Ghana (Agyepong 1992; Asenso-Okyere & Dzator 1997), which is usually perceived as a threat. However, e.g. for some adults with blood in stool, it may be possible that fear of much more serious disease such as colon cancer was the reason for seeking health care. It is hoped that in future studies the reasons for taking a particular health care action would be explored in addition to reasons for not visiting a hospital or clinic.

In an era of financial stringency, a more realistic formulation of health policies and programmes requires a better understanding of the determinants of health care-seeking behaviour. Several studies about the effect of cost recovery policies introduced in the early 1990s in Ghana and elsewhere showed that the *cash and carry* system, which was intended to recover cost, led to a drop in attendance of hospitals, health centres and clinics (Biritwum 1994; Wyss *et al.* 1996) and a concomitant increase in self-medication and other cost savings (Asenso-Okyere *et al.* 1998). It

was therefore not surprising that for most subjects in the lower socio-economic class at Kokoetsekope, the reason for not visiting a clinic/health centre was, 'Do not have the money'. The rate of health care seeking did not differ between the two socio-economic groups though. The observation in this study that fathers were the main financial providers for health care suggests that mothers' perception and their roles may not necessarily lead to health care for the child if the father's perception is poor. Obviously, the role of the financial provider, mainly fathers, for health care is crucial and must be considered seriously in health education programmes.

The finding that some teenagers, particularly those not in school and mostly boys, started financing their health care at a very early age (14 years) may in part explain their unusually low tendency to visit clinics or health centres. Child labourers may not earn enough to finance their health care. Weighed against other diseases of high debility, money may not be spent to seek health care for a mild recurring disease. The implications are serious although, as severe pathology is usually a consequence of long-term infection. This suggests that teenagers who usually have high intensity (and high frequency of signs and symptoms) may also suffer from more severe pathology for not receiving treatment. Teenagers therefore remain a major challenge to the success of health care integrated schistosomiasis control.

Self-medication is a worldwide phenomenon (Abosede 1984; Kloos *et al.* 1987; Haider & Thaver 1995) and was practiced by a high percentage of our subjects. This observation could in part be explained by factors such as patient's ability to pay and availability of diagnostics/therapeutics in health facilities. Lack of praziquantel in most peripheral health facilities in endemic areas of Ghana was reported in a recent survey (Van der Werf *et al.* 2003). Nonetheless, in the current study unavailability of drugs in the health care facilities was rarely mentioned as a reason for not attending a health facility. Other factors such as the quality of service delivery and overall time spent to seek care are probable causes. The average distance to health facilities was short and may not negatively affect attendance. Nevertheless, the high self-medication rate is an indication of health awareness that could be explored towards the integrated approach to schistosomiasis control.

The observation that schistosomiasis-related signs and symptoms were either reported to health facilities as first option followed by self-medication or visiting a clinic/health centre after self-medication has serious implications. First of all, self-medication after regular health care suggests that patients did not receive adequate treatment. Nevertheless, engaging in self-medication before visiting a clinic or health centre also suggested that regular health care remained a final option. The potential role that the health system can play in health care delivery was revealed by the preference of allopathic self-medication to herbal or traditional treatment. However,

the failure of many subjects with blood in urine and painful urination to take action is a challenge for schistosomiasis control by passive case detection.

The overall low rate of visiting health care facilities by patients may not seem very encouraging for integrated control. However, a hospital visit is expected to be selective towards those with heavy infections; on average 20% that visited a health care facility with early symptoms may represent most of those at risk of developing severe consequences of schistosome infection later (e.g. kidney problems, portal hypertension or vomiting blood). A study in rural Cameroon showed selective hospital visit for haematuria by high intensity cases that formed only 13% of the overall infection in the population (Slootweg *et al.* 1995). Ideally, an overall judgment of the prospects of integrated control by passive case finding requires prospective cohort studies of considerable length of time incorporating complex issues such as the natural history of development of pathology and morbidity, the intermittent nature of some of the signs/symptoms and insensitive parasitological diagnosis. As such follow-up studies are impossible to conduct for ethical reasons, the use of simulation models is probably the only way to adequately study these complex issues. The potential to receive adequate treatment perhaps is not as bad as reflected by the low rate of visiting hospitals or clinics, as some of those who engaged in orthodox self-medication may have received praziquantel elsewhere. Furthermore, the high preference for orthodox self-medication is a key potential to explore to increase the utilization of the regular health system. Health education, for example, could trigger those who apparently find their symptoms important enough to take action to go to a health care facility. Also, health education may raise awareness of many individuals with, e.g., blood in urine or blood in stools that did not take any action. Obviously, there is a need to make praziquantel available and accessible to endemic communities at the same time with health education.

Our study has shown that over 90% of those that self-medicated or visited chemical shops for treatment did not receive praziquantel. At the same time, there was no known traditional medicine for treating schistosomiasis-related symptoms. This raises serious public health concern as self-medication seems less likely to help in morbidity control of schistosomiasis. Also, given that knowledge about the cause of schistosomiasis-related symptoms was poor and majority of patients that visited health facility or chemical shop did not have any idea about the kind of prescription or treatment provided, calls for additional efforts such as health education to address this problem. It should be clear that successful integration of schistosomiasis control activities within the existing health care delivery system should target patients and health care providers alike. Particularly, the knowledge of health care providers at the peripheral levels is crucial to the success of the integrated concept because

of the changing pattern of schistosomiasis in Ghana. In the preliminary survey to select a suitable field site for this study, it was noted that case-specific records in most health facilities in the country rarely differentiated between urinary and intestinal schistosomiasis. Most reported cases of schistosomiasis were simply registered as 'bilharzia'. This may be so because of perceived predominance of urinary schistosomiasis based on earlier distribution (Rambajan 1994). The pattern is changing as an intense focus of transmission was reported in northern Ghana (Amankwa *et al.* 1994), and the prevalence of intestinal schistosomiasis by microscopy in the present study area was 78%. In Egypt, a similar observation was made when health care personnel continued to focus on *S. haematobium* at a time when *S. mansoni* had become the predominant species (el Katsha & Watts 1995). Consequently, health personnel and persons at risk must be sensitive to the tremendous variations that exist in the clinical presentation of schistosomal infection. Equipment for parasitological diagnosis and supply of praziquantel are essential.

The low rate of reported health care facility visiting for schistosomiasis-related signs and symptoms could be attributed to several factors including the perceived seriousness of the disease, availability of money, seasonal effects, drug peddlers who visit endemic communities and drug sales at chemical shops. Furthermore, the quality of service, availability of diagnostics and therapeutics, and perceived effectiveness of treatment may influence the decision to visit a clinic or health centre. Hewlett and Cline (1997), for example, identified severity of signs and symptoms as an important determinant of health care visiting for urinary schistosomiasis in Cameroon. There is the need for further studies to elucidate these determinants in the study area.

This study has identified a number of factors that should be emphasized in attempts towards schistosomiasis integrated control. However, in view of the extreme sensitivity to inaccurate recall in health-seeking behaviour studies based on self-perceived morbidity reporting, more detailed studies incorporating case-specific records are in progress to further elucidate and validate the identified factors.

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Chapter 6

Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana

Danso-Appiah A, Stolk WA, Bosompem KM, Otchere J, Looman CNW, Habbema JDF, de Vlas SJ. Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana. *(submitted)*.

6.1 Abstract

Schistosomiasis causes long-term illness and significant economic burden. Morbidity control through integration within existing health care delivery systems is considered a potentially sustainable and cost-effective approach, but there is paucity of information about health seeking behaviour. A questionnaire-based study involving 2,002 subjects was conducted in three regions of Ghana to investigate health seeking behaviour and utilization of health facilities for symptoms related to urinary (blood in urine and painful urination) and intestinal schistosomiasis (diarrhea, blood in stool, swollen abdomen and abdominal pain). Fever (for malaria) was included for comparison. Only 40% of patients with urinary symptoms sought care compared to >70% with intestinal symptoms and >90% with fever. Overall, about 20% of schistosomiasis-related symptoms were reported to a health facility (hospital or clinic), compared to about 30% for fever. Allopathic self-medication was commonly practiced as alternative action. Health care seeking was relatively lower for patients with chronic symptoms, but if they took action, they were more likely to visit a health facility. In a multivariate logistic regression analysis, perceived severity was the main predictor for seeking health care, or visiting a health facility. Age, socio-economic status, somebody else paying for health care, and time for hospital visit occasionally showed a significant impact, but no clear trend. The effect of geographic location was less marked, although people in the central region, and to a lesser extent the north, were usually less inclined to seek health care than people in the south. Perceived quality of health facility did not demonstrate impact. Perceived severity of the disease is the most important determinant of seeking health care or visiting a health facility in Ghana. Schistosomiasis control by passive case-finding within the regular health care delivery looks promising, but the number not visiting a health facility is large and calls for supplementary control options.

6.2 Author summary

The World Health Organization recommends that long-term benefit of schistosomiasis control should include treatment in local health facilities. This means that patients should visit a hospital or clinic with their complaints. However, little is known about whether they do so. We conducted a study in three regions of Ghana and interviewed two thousand people about whether they recently had schistosomiasis-related symptoms such as blood in urine or blood in faeces, and what they had done with it. We included fever (mostly caused by malaria) for comparison. We found that 40% of patients with urinary symptoms sought care compared to 70% of those with intestinal symptoms and 90% with fever. Overall, only 20% of all schistosomiasis-related symptoms were reported to a hospital or clinic, compared to 30% for fever. Self-medication with orthodox medicines was the main alternative. Our study showed that the most important determinant for seeking health care or visiting a health facility is perceived severity of the symptom. Factors such as age, sex, socio-economic status and geographic region showed no impact or a clear pattern. We conclude that many schistosomiasis patients do not visit a health facility, the only place with effective drugs, necessitating additional control measures.

6.3 Introduction

Schistosomiasis leads to chronic ill health and significant economic burden (Engels & Savioli 2006; Hotez *et al*. 2006; Steinmann *et al*. 2006; King and Dangerfield-Cha 2008). *Schistosoma haematobium* and *S. mansoni* are widespread in Africa causing urinary and intestinal schistosomiasis, respectively. Both species are found in Ghana, sometimes as mixed infection in the same person. For most people who are repeatedly exposed, the severity of disease depends upon the intensity of infection. Haematuria (blood in urine) and dysuria (painful urination) are the main early symptoms of urinary schistosomiasis and diarrhoea, blood in stool and abdominal pain for intestinal schistosomiasis. Over 70% of infected children show one or more early symptoms and signs of disease (Mott *et al*. 1983; Olds & Dasarathy 2000). Adults, who usually have light infections, are often asymptomatic but some develop late pathology after prolonged infection.

After the introduction of praziquantel in the late 1970s, the World Health Organization in association with ministries of health of several endemic countries met in 1983 to assess viable control strategies. The high price of praziquantel in those days led to the endorsement of morbidity control with emphasis on treating individuals with early symptoms of the disease or having high egg counts (WHO 1985). As the development of pathology and disease are closely associated with intensity and duration of infection, the assumption was that treating these cases will prevent most late-stage complications which are insidious and occur many years after the infection. This control strategy was reviewed by the WHO Expert Committee in 1991 and proved to be effective in vertical control programmes, but sustainability was identified as a major problem due to the over-reliance on foreign donors (WHO 1993). To be sustainable, there should be a prominent role of the existing health care delivery system that builds on local structures and capacity, called a horizontal approach (WHO 1998, 2002).

Guyatt and Evans (1992) pointed out that the community's perception of the disease and socio-economic factors are particularly important in ensuring effectiveness in control strategies that rely on passive case-finding. For seeking health care, people must consider the symptoms a health threat and have resources available (Shaw 2001). Health care seeking behaviour is not only a matter of knowledge about the cause and treatment of the disease, but also of perceived seriousness and duration, cultural practices and socio-economic status (Shaikh & Hatcher 2007). Perceived quality of the health care expected, availability and cost of medicine, distance to hospital, and user fees charged also influence hospital visit (Shaikh *et al*. 2008). Therefore, understanding peoples' health-seeking behaviour and factors influencing

their decision to self-report with schistosomiasis-related signs and symptoms is highly relevant to policymakers towards integrated control within the regular health services.

Paucity of information about health care seeking behaviour for schistosomiasis symptoms led us to conduct our previous study (Danso-Appiah *et al*. 2004). The results showed that around 70% with blood in urine or painful urination did not seek health care. Symptoms associated with intestinal schistosomiasis (diarrhoea, blood in stool and abdominal pain) and also fever usually led to health care although self-medication with allopathic drugs was commonly practiced. On average 20% of schistosomiasis-related signs and symptoms were reported to health facilities. Teenagers consistently showed lower tendency to take action for their symptoms than children under 10 years and adults. Socio-economic status and duration of symptoms did not appear to influence health-seeking behaviour, and lack of money (43%) and symptom perceived as not serious enough (41%) were the commonest reasons for not visiting a clinic.

We conducted a larger study in multiple locations in Ghana to learn whether patterns of health seeking behaviour are consistent across other parts of the country, get better insight into regional characteristics, and to enable formal analysis of determinants of action. The study also investigated the effect of new factors namely, geographic location, distance and perceived quality of health facility.

6.4 Materials and methods

Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Noguchi Memorial Institute for Medical Research (Accra) and Erasmus MC (Rotterdam). Thereafter, a detailed plan of the study and its objectives were submitted to the Ethical Committee of the Ministry of Health (Ghana) for approval, which was granted. The purpose of the study and its objectives were explained to local authorities, opinion leaders and community members at a durbar. At the beginning of each interview the purpose of the study was explained to participants again and informed oral consent sought before the questionnaire was administered. For children, a parent or guardian had to give consent before they were interviewed. All participants were assured about confidentiality of information obtained from them. Only individual codes were used in the electronic documents and the original documents on paper were stored in a safe place.

Health care delivery in Ghana

Health care delivery in Ghana is based on the Primary Health Care concept (WHO, 1978). At least one government-owned hospital is located in each district capital and staffed with one or more qualified medical doctors, nurses, pharmacists, laboratory technicians, auxillary nurses and other support personnel. The district hospitals deal with all cases except specialised care, and serious cases are referred to the regional tertiary hospitals. There are also a number of health centres mostly without laboratory facilities in the sub-districts which are manned by a medical assistant or a nurse. There are also private clinics and chemical shops/pharmacies in the district and sub-district capitals. In the health facilities in our study sites treatment for schistosomiasis-related symptoms was mostly based on signs and symptoms (presumptive treatment) and the system of payment during the period of the study was cash and carry (out of pocket payment) where a patient was required to make full payment for consultation before treatment was provided. Laboratory tests, if indicated, were referred. Within the cash and carry system, essential drugs were mostly kept in the health facilities for purchase, but patients had to obtain other drugs from private pharmacies.

Study area and population

This questionnaire-based study was conducted in 2002-2003 in three different sites of the country (south, central and north), which reflect Ghana's ethnic and cultural diversity and distribution of general infrastructure that may influence health seeking behaviour (see Figure 6.1).

The main criteria for selecting a village for inclusion in the study were; 1) the village must be endemic for either urinary or intestinal schistosomiasis or both, 2) there must be a health facility where at least 80% of the inhabitants would visit when ill or experiencing minor ailments, and 3) the village should have a stable population where new entrants moving into or old inhabitants leaving the population is minimal. From the south we selected two villages, relatively near and far from health facilities utilized by both villages to test the impact of distance on health seeking behaviour.

One village, Biu, along the Tono irrigation site (labelled A in Figure 6.1) was selected from the north dry semi-desert part of the country: Biu had about 1200 inhabitants and prevalence of 56% and 48% for intestinal and urinary schistosomiasis, respectively. There is one government health centre in Biu and the referral hospital is located in the district capital (Navrongo) about 20 km away. There are no chemical shops in Biu and patients including schistosomiasis-related cases obtain most of their drugs prescribed to them from private drug stores in Navrongo. The main occupation of adults aged over 18 years is farming on the irrigation fields, but some

also rear cattle and sheep. The vast majority of adult females engage in petty trading but a reasonable number also farm. The Tono Lake formed as a result of the dam is used for drinking, bathing, domestic activities, fishing and farming thereby making the lake the main source of the infection. Amankwah et al. (1994) provides a detailed description of the Biu study area.

Figure 6.1 Map of Ghana showing the study areas.

From the Ashanti region in the central tropical forest of Ghana, two adjacent villages endemic for only urinary schistosomiasis were selected (labelled B in Figure 6.1): Kyereyase (about 1200 inhabitants and prevalence >71%) and Nyamebekyere (about 300 inhabitants and prevalence >65%). The demography and epidemiology of these two villages were so similar that we considered them as one in our analysis. There was no health facility or chemical shop in these villages, but outreach services delivered by public health nurses from the district hospital were offered in Kyereyase. The nearest health facility utilized by some patients from the two villages was a private clinic located in Nerebehi about 3 km from Kyereyase and 6 km from Nyamebekyere.

The district hospital located in Nkawie (the district capital) about 5 km from Kyereyase also serves as the referral centre for cases from most private clinics and health centres in the surrounding towns and villages. Some schistosomiasis-related cases from Kyereyase and Nyamebekyere are reported to health facilities in the regional capital in Kumasi about 7 km away. The two study villages are separated by the River Offin, which is the main source of water for drinking, bathing and domestic activities. Children swim in the river on regular basis making the river the main source of the infection. Kyereyase is accessible by road but the inhabitants of Nyamebekyere live behind the river and have to walk through the forest to cross River Offin midway by a canoe in order to join a vehicle from Kyereyase to nearby commercial towns or health facilities. Cocoa and rice are the main cash crops cultivated by the farmers in these villages.

Two villages were selected from the Greater Accra region in the south coastal savannah belt, which are endemic for both urinary and intestinal schistosomiasis (labelled C in Figure 6.1): Manheim (about 3000 inhabitants and prevalence (60% and 56%) for intestinal and urinary schistosomiasis, respectively and Tomefa (about 1500 inhabitants and prevalences of 72% and 70%). Manheim had two private clinics where some schistosomiasis-related cases reported for treatment and one chemical shop where individuals bought their drugs. Tomefa is about 10 km from the nearest health facility and has no chemical shop. The two villages utilize the same health facilities in Manheim and Kasoa, a nearby commercial centre about 1 km from Manheim. There are two public health centres and about ten private clinics in Kasoa, but most people from Manheim and Tomefa with minor ailments including schistosomiasis-related symptoms utilize the government-owned health facilities. These health facilities mostly refer cases to the nearest government-owned polyclinics in Accra, about 10 km away. The inhabitants of Tomefa visit the health facilities in Manheim and Kasoa either by a car or canoe. The distance is variable depending on the medium of transport used: about 5 km by a canoe and 10 km by car. However, boats and canoes are rarely used as means of transport by non-fishermen including women and children because of the dangers associated with it. The main occupation of adult men in these villages is fishing whilst the women are mostly petty traders. The inhabitants of these villages fetch water from the lake for drinking, bathing and domestic activities whilst children swim in it on regular basis making the lake the main source of schistosomiasis infection. Manheim and Tomefa are located in the same area as our earlier study along the Densu Lake (Danso-Appiah et al. 2004).

Data collection

Copies of approved ethical clearance from the Ministry of Health (Ghana) were sent to all concerned parties and authorities including District Chief Administrators and Directors of Health Service. Opinion leaders, household heads and community members were first informed about the study at community durbars and their consent sought. A detailed plan of the study was outlined and discussed with all the inhabitants. Written consent was not sought because of high levels of illiteracy of the study population. The IRB approved the use of oral consent prior to the start of the study. At the beginning of each interview the purpose of the study was explained to participants and oral consent sought. For children, a parent or guardian gave consent. Names of participants were recorded in interview books and boxes to document consent were ticked when consent was given, a cross otherwise. We did not encounter problems or individuals who did not want to participate in the study. Each study village was mapped, divided into sectors based on topography and closeness to the source of infection, houses numbered and each individual registered according to household. Households were randomly selected using computer generated random numbers. The questionnaire used in our earlier study (Danso-Appiah *et al*. 2004) was slightly adapted and administered to all inhabitants in the selected households. Each subject was assigned an identification code defining the village, sector, house number and serial number.

The questionnaire was made up of a section on date of interview, name of interviewer, start and end time of interview, questionnaire book number, house number, individual serial number and identification code; a demographic section including name, sex and age of subjects; decision-making indicators such as who requests health care, who provides money for health care, who accompanies the patient when visiting the hospital; socio-economic indicators such as level of education, occupation and property owned; indicators of schistosomiasis-related signs and symptoms such as symptom currently present or present during the past one week or one month, duration and severity; action taken for each symptom and the name of health facility last visited, perceived quality of care received and the length of time spent (including travel, waiting and consultation) when they visited this health facility. Symptoms were categorized as acute when present for up to one week, and chronic otherwise. The three severity classes mild, moderate and severe were based on self-reporting.

The signs and symptoms covered by the questionnaire were: blood in urine and painful urination (for urinary schistosomiasis), and blood in stool/bloody diarrhoea, diarrhoea, abdominal pain and swollen abdomen (for intestinal schistosomiasis). These signs and symptoms are only suggestive, but not necessarily, due to

schistosomiasis. Fever (for malaria) was added as a serious and debilitating disease for comparison. Questions relating to signs and symptoms were asked in a random order. The socio-economic status of individuals was assigned by using the status of the household to which they belong. Three possessions (car, fridge and television) were selected as indicators of relatively high socio-economic status of a household. Any household owning one or more of these was considered as high socio-economic class, otherwise low.

Registered individuals from the randomly selected households in each village were interviewed, with parents or guardians answering for children aged under six years. Potential respondents for individuals who could not answer the questions for themselves, mostly children, were preferentially ranked as follows: mother, father, guardian (aunt, uncle or other close relatives). Registered individuals who were not present during the interview and subsequent follow-up visits were classified as permanently missing and excluded from the study. To minimize variability, the questionnaire, which took an average of 20 minutes each to administer, was applied by two trained interviewers who also did the interviews for our earlier study (Danso-Appiah *et al*. 2004).

Data management and statistical analysis

The data were double entered. The first entry was done manually using Epi-Info (version 6.04), and the second electronically using an Electronic Scanning Data Entry Machine. The two resulting datasets were compared and cleaned using Excel. In case of discrepancies, the hard copies were consulted and the necessary corrections made. Copies of the questionnaire books and back-ups of the electronic data were kept at the Noguchi Memorial Institute for Medical Research in Ghana and the Department of Public Health, Erasmus MC, Rotterdam. Descriptive and logistic regression analyses were done using SPSS version 15.0.

Using logistic regression we tested the impact of various factors on the tendency to take any action (i.e. to self-medicate or visit a health care facility) for each symptom separately, and on the tendency to visit a health facility (hospital or clinic) as first action given any action. First, univariate analyses were conducted for the following factors and interaction terms: age, sex, location, socio-economic status (SES), perceived severity and duration of symptom, whether 'self' or 'other' provided money for health care, perceived quality of health care, time spent in obtaining care from a health facility and the interaction terms- age×sex and severity×duration of symptom. Only these two interaction terms seemed relevant and sometimes tested significant in univariate analysis. The impact of distance to health facility was tested as part of location using the comparison between Tomefa (far) and Manheim (near).

Subsequently, we conducted multivariate analyses to obtain adjusted ORs. For each symptom, all variables showing an overall $p<0.20$ in the univariate analysis were selected for inclusion in the multivariate analysis as recommended by Hosmer & Lemeshow (1989). No further backward or forward selection procedures were conducted, but interaction terms were removed, because their effects were negligible in the multivariate analyses.

In subsequent steps, we grouped all symptoms together and re-analyzed the factors that influenced taking any action or visiting the hospital as first action. For this purpose, we did a multi-level analysis with bootstrapping, including a random factor component to account for repeated observations from the same individuals. These analyses resulted in significant impact of the interaction of various key factors with type of symptom, indicating it was not appropriate to combine different symptoms and analyse as one. Therefore, we report results for each symptom separately.

6.5 Results

In total 2,002 individuals were interviewed, coming from 52 households (with an average of 6 members) from north (Biu), 75 (13) from central (Kyereyase/ Nyamebekyere), 70 (8) from south (Tomefa), and 81 (8) from south (Manheim). There were 1010 females and 992 males of all ages, of which 614 were children under 10 years, 466 teenagers and 922 adults. Educational level among individuals aged over 15 years was low, 858 (77%) had no or only elementary education and < 5% had attended a senior high school or had tertiary education, with the rest having up to junior high school (slightly above elementary school). The vast majority of adult men were farmers, fishermen or low-income earners, whilst most of the women were farmers, petty traders or both.

Age and level of education did not differ markedly between the different study sites (Table 6.1). However, sex and socio-economic status showed marked differences. The percentage of males in Tomefa (58%) differed from the other villages (42-50%), whilst relatively high socio-economic status was rare in the north (5%) compared to central (21%) and south (47-57%). The decision making process for obtaining health care did not differ between locations. The proportion of patients reporting to take more than half a day in visiting a health facility is much lower in the north than in other regions (34% vs. 64-98%). When asked what they would do if they had blood in urine, diarrhoea, blood in stool or fever over 96% reported they would seek health care.

Table 6.1 Characteristics of the study populations and indicators of health seeking behaviour across different locations in Ghana.

Factor	North	Central	South (Tomefa)	South (Manheim)
Subjects interviewed	300	510	525	667
Prevalence of infection				
% *Schistosoma mansoni*	56	-	72	60
% *S. haematobium*	48	71	70	56
Demographic characteristics				
Males (%)	125 (41.7)	254 (49.8)	302 (57.5)	311 (46.6)
Children < 15 years (%)	126 (42.0)	247 (48.4)	215 (41.0)	295 (44.2)
High education (%)*	5 (1.7)	10 (2.0)	19 (3.6)	24 (3.6)
High SES (%)#	16 (5.3)	106 (20.8)	246 (46.9)	380 (57.0)
Decision making process to seek health care				
Someone else requesting for health care	121 (40.3)	271 (53.1)	290 (55.2)	367 (55.0)
Someone else paying for health care (%)	100 (33.3)	130 (25.5)	170 (32.4)	223 (33.4)
Health facility indicators				
Perceived HF as good (%)†	244 (95.7)	339 (92.6)	232 (69.3)	349 (80.4)
≥ ½ a day for visiting HF (%)	77 (34.5)	269 (97.8)	190 (79.2)	214 (64.3)
Tendency to take action‡				
Blood in urine (%)	294 (98.0)	500 (98.0)	504 (96.0)	642 (96.3)
Diarrhoea (%)	297 (99.0)	502 (98.4)	499 (95.0)	642 (96.3)
Blood in stool (%)	295 (98.3)	505 (99.0)	501 (95.4)	642 (96.3)
Fever (%)	297 (99.0)	506 (99.2)	506 (96.4)	640 (96.0)
Reporting signs/symptoms				
Blood in urine (%)	51 (17.0)	141 (27.6)	106 (20.2)	117 (17.5)
Painful urination (%)	34 (11.3)	107 (21.0)	132 (25.1)	118 (17.7)
Diarrhoea (%)	33 (11.0)	95 (18.6)	88 (16.8)	93 (13.9)
Blood in stool (%)	50 (16.7)	77 (15.1)	173 (33.0)	155 (23.2)
Swollen abdomen (%)	6 (4.4)	42 (31.1)	42 (31.1)	45 (33.3)
Abdominal pain (%)	74 (24.7)	162 (31.8)	178 (33.9)	154 (23.1)
Fever (%)	143 (47.7)	255 (50.0)	246 (46.9)	244 (36.6)
Health seeking behaviour (any action), for those reporting signs/symptoms				
Blood in urine (%)	15 (29.4)	33 (23.4)	50 (47.2)	71 (60.7)
Painful urination (%)	13 (38.2)	34 (31.8)	77 (58.3)	67 (56.8)
Diarrhoea (%)	25 (75.8)	78 (82.1)	77 (87.5)	68 (73.1)
Blood in stool (%)	32 (64.0)	44 (57.1)	126 (72.8)	97 (62.6)
Swollen abdomen (%)	3 (50.0)	18 (42.9)	30 (71.4)	35 (77.8)
Abdominal pain (%)	60 (81.1)	137 (84.6)	135 (75.8)	118 (76.6)
Fever (%)	134 (93.7)	238 (93.3)	229 (93.1)	219 (89.8)

Table 6.1 Continued

Factor	North	Central	South (Tomefa)	South (Manheim)
Health seeking behaviour: visiting health facility (hospital or clinic) as first action for those reporting signs/symptoms				
Blood in urine (%)	2 (3.9)	7 (5.0)	20 (18.9)	23 (19.7)
Painful urination (%)	4 (11.8)	10 (9.3)	31 (23.5)	24 (20.3)
Diarrhoea (%)	7 (21.2)	10 (10.5)	29 (33.0)	19 (20.4)
Blood in stool (%)	7 (14.0)	3 (3.9)	40 (23.1)	25 (16.1)
Swollen abdomen (%)	0 (0.0)	6 (14.3)	18 (42.9)	11 (24.4)
Abdominal pain (%)	16 (21.6)	18 (11.1)	41 (23.0)	29 (18.8)
Fever (%)	37 (25.9)	45 (17.6)	83 (33.7)	67 (27.5)

* High educational level means attended senior secondary school or tertiary education such as polytechnic and university.

Three properties car, fridge and television were used as indicators for high socio-economic status.

†The denominators do not include those who said they had not visited a health facility or new entrants who had not yet visited a health facility.

‡ Refers to the question what they would do if confronted with the following symptoms. For those aged under six years or older who could not answer the questions themselves, a parent or guardian answered for them

Many of the 2,002 subjects reported to have experienced schistosomiasis-related symptoms in the past month: 28.4% reported abdominal pain, 22.7% blood in stool, 20.7% blood in urine, 19.5% painful urination, 15.4% diarrhoea and 6.7% swollen abdomen. Fever was reported by 44.4% of the population. All seven symptoms were reported in each study site, although *S. mansoni* is not present in the central study area (Table 6.1). The proportions of people with these symptoms did not differ markedly between study sites, except for swollen abdomen, which was reported much less in the north (4%) than in the other areas (31-33%). Overall, patients in the south showed higher tendency to take action or visit a health facility for their signs or symptoms than patients from the central or north.

Figure 6.2a shows main actions taken for schistosomiasis-related symptoms and fever. Doing nothing, self-medicating and visiting a health facility were commonly reported. The large majority of people with blood in urine (60%) or painful urination (>50%) did not seek health care, whereas >90% with fever and about 80% with diarrhea and abdominal pain did take action, mostly self-medication with allopathic drugs. Overall, about 20% schistosomiasis-related symptoms (17% of urinary and 21% of intestinal symptoms) were reported to health facilities as first action,

and the percentage did not differ much across symptoms. The proportions visiting a health facility for fever (30%) did not differ appreciably from those visiting with schistosomiasis-related symptoms (20%) (Figure 6.2b). Multiple actions for a symptom were practiced with some of those self-medicating subsequently visiting a health facility as a second or third alternative and vice versa. The tendency to seek health care was lowest for the symptoms with chronic characteristics (blood in urine, painful urination, swollen abdomen), but when these patients do something, they are more likely to go to the health facility.

The multivariate analysis revealed that people more often took action when they perceived their symptom as severe. This effect was consistent for all the symptoms (Table 6.2). Age, socio-economic status, someone else providing money for health care showed some effect, but no clear pattern. Sex, duration of symptom, perceived quality of health facility and time for visiting health facility did not demonstrate a significant impact. Usually, symptoms more often led to action for young children (aged 0-9) than for teenagers and to a lesser extent for adults. Although this effect was usually not significant, the direction was fairly consistent. Similarly, the tendency to take action for symptoms is higher for high socio-economic status or if someone other than the respondent paid for health care. The effect of location is less marked, although people in the central region were less inclined to seek health care than in the south, and to a lesser extent north.

Table 6.3 shows the determinants of visiting a health facility (hospital or clinic) as first action, in the group of people taking action. Effects are clearest for fever, but are also rather consistent over other symptoms. The direction of the effects is usually the same as described in Table 6.2, but patterns are more pronounced. Severe symptoms consistently led to an increased tendency to visit a hospital. There were some differences in health seeking behaviour variables across study sites: the people in Tomefa (far from health facility) were more likely to go to the health facility than in Manheim (near), while those in the central region were less likely to do so. Here, duration of symptoms showed effect: patients were less likely to visit the hospital as first action for acute symptoms than for chronic symptoms. The effects of age and socio-economic status were in the same direction as for any action. The other factors tested did not show consistent effects.

Self medication in figure 6.2b includes herbal treatment, orthodox medicines, and spiritualist care.

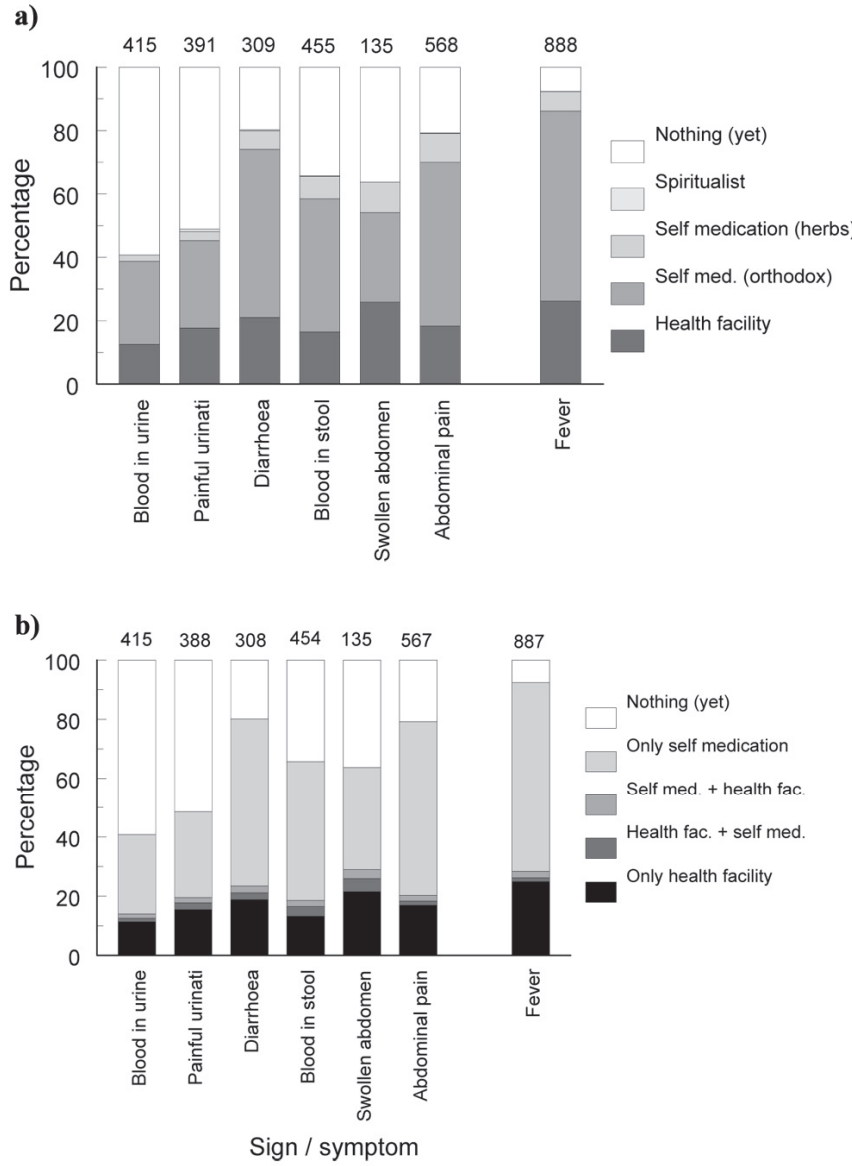

Figure 6.2 Reported action taken about schistosomiasis-related signs and symptoms (a) first action only and (b) first and second actions (first action followed by second).

Table 6.2 Odds ratios (95% CI) resulting from multivariate logistic regression analysis summarizing overall patterns towards any health care action for different schistosomiasis-related signs/symptoms. The empty cells indicate factors resulting in p>0.2 from the univariate analysis and that were hence not included in the multivariate model. INF means infinite, i.e. > 999, QHF indicates perceived quality of health facility (hospital) visited in the last instance and THF is time spent visiting the health facility.

Factor	Blood in urine (n = 415)	Painful urination (n = 391)	Diarrhoea (n = 309)	Blood in stool (n = 455)	Swollen abdomen (n = 135)	Abdominal pain (n = 568)	Fever (n = 888)
Age 0-9 vs 20+ years	2.8 (0.5-15)	1.2 (0.4-3.2)	2.2 (0.7-7.5)*	0.84 (0.42-1.7)	0.34 (0.05-2.2)	1.8 (0.8-4.2)*	3.4 (1.5-7.7)**
Age 10-19 vs 20+ years	3.2 (0.6-17)*	0.67 (0.26-1.7)	0.61 (0.19-1.9)	0.36 (0.18-0.73)**	0.56 (0.10-3.1)	1.5 (0.6-3.4)	0.63 (0.35-1.1)*
Female vs male	0.85 (0.41-1.7)			0.81 (0.52-1.3)			0.61 (0.36-1.0)*
SES high vs low	1.1 (0.5-2.4)	2.1 (1.0-4.2)**					1.8 (1.0-3.2)*
North vs South (Manheim)	0.31 (0.09-1.1)*	0.68 (0.21-2.2)	1.0 (0.3-3.3)	1.7 (0.8-3.4)*	(0.0-INF)	0.96 (0.29-3.1)	
Central vs South (Manheim)	0.14 (0.05-0.41)**	0.62 (0.26-1.5)	0.88 (0.33-2.3)	0.91 (0.50-1.7)	0.14 (0.02-1.1)*	0.64 (0.24-1.7)	
South (Tomefa) vs South (Manheim)	0.43 (0.16-1.2)*	1.2 (0.5-2.8)	2.7 (0.8-8.9)*	2.1 (1.2-3.4)**	0.41 (0.05-3.3)	1.0 (0.4-2.7)	
Moderate vs mild	0.81 (0.35-1.8)	1.1 (0.5-2.3)	1.0 (0.4-2.5)	2.0 (1.2-3.2)**	2.0 (0.4-11)	3.5 (1.6-7.9)**	2.3 (1.3-4.0)**
Severe vs mild	3.7 (1.4-9.8)**	1.6 (0.8-3.5)	4.0 (1.2-13)**	3.3 (1.7-6.4)**	6.4 (1.0-42)*	4.5 (1.8-11) **	4.6 (2.2-9.8)**
Acute vs chronic	0.66 (0.17-2.6)			1.5 (0.9-2.4)*	1.3 (0.1-16)		
Other vs self paying for health care	7.6 (1.2-46)**	1.7 (0.6-4.7)	1.7 (0.5-6.1)	1.0 (0.5-2.1)			
QHF somewhat good vs good	1.2 (0.5-2.9)	0.94 (0.43-2.1)	2.6 (0.7-9.7)*			0.64 (0.28-1.5)	
THF less than 2 hours vs ≥ ½ day‡	1.2 (0.5-3.0)	1.4 (0.6-3.4)			1.7 (0.2-15)	1.6 (0.6-4.1)	

* Factors with an effect of 0.05 ≤ P< 0.20.

** Factors with an effect of P < 0.05.

‡There were no observations with THF between 2 and 4 hours

Table 6.3 Odds ratios (95% CI) resulting from multivariate logistic regression analysis summarizing overall patterns of visiting a health facility (hospital or clinic) as first action among individuals taking any health care action for different schistosomiasis-related signs/symptoms (see Table 6.2 for further explanation).

Factor	Blood in urine (n = 52)	Painful urination (n = 69)	Diarrhoea (n = 65)	Blood in stool (n = 75)	Swollen abdomen (n = 35)	Abdominal pain (n = 104)	Fever (n = 232)
Age 0-9 vs 20+ years		0.39 (0.10-1.5)*	3.0 (1.5-6.0)**	2.2 (0.9-5.6)*		1.5 (0.8-3.1)	1.5 (1.0-2.4)*
Age 10-19 vs 20+ years		0.49 (0.15-1.5)	0.97 (0.41-2.3)	2.5 (0.9-6.7)*		1.3 (0.6-2.7)	0.62 (0.36-1.1)*
Female vs male		1.8 (0.6-5.8)					1.4 (1.0-2.0)*
SES high vs low		1.2 (0.5-2.8)		1.7 (0.8-3.9)*		2.1 (1.1-4.1)**	1.5 (1.0-2.1)**
North vs South (Manheim)	0.18 (0.03-0.97)**	0.67 (0.15-3.0)	1.4 (0.5-4.0)	1.7 (0.5-6.7)	(0.0-INF)	1.5 (0.6-4.1)	1.0 (0.6-1.8)
Central vs South (Manheim)	0.16 (0.04-0.65)**	0.70 (0.20-2.4)	0.59 (0.24-1.4)	0.29 (0.07-1.3)*	0.34 (0.11-1.1)*	0.82 (0.33-2.0)	0.61 (0.38-1.0)**
South (Tomefa) vs South (Manheim)	1.0 (0.4-2.9)	1.5 (0.6-3.9)	2.4 (1.2-5.1)**	2.5 (1.0-6.4)**	3.3 (1.1-9.8)**	1.7 (0.8-3.6)*	1.6 (1.0-2.4)**
Moderate vs mild	1.2 (0.4-3.7)	1.5 (0.5-4.3)	1.1 (0.5-2.5)	1.6 (0.6-3.8)		1.0 (0.5-2.1)	1.1 (0.7-1.7)
Severe vs mild	2.1(0.7-6.6)*	1.6 (0.6-4.3)	2.5 (1.1-5.4)**	3.3 (1.2-9.1)**		2.3 (1.1-4.7)**	3.0 (1.9-4.5)**
Acute vs chronic			0.33 (0.18-0.60)**	0.29 (0.10-0.84)**		0.32(0.18-0.58)**	0.50 (0.35-0.69)**
Other vs self paying for health care							0.61 (0.37-0.98)**
QHF somewhat good vs good					1.9 (0.6-5.8)		
THF less than 2 hours vs ≥ ½ day‡	1.6 (0.6-4.5)	2.8 (1.1-7.5)**		0.37 (0.14-0.96)**		1.1 (0.5-2.1)	

* Factors with an effect of $0.05 \leq P < 0.20$.

** Factors with an effect of $P < 0.05$.

‡ There were no observations with THF between 2 and 4 hours

6.6 Discussion

The mechanisms driving health seeking behaviour are complex. This questionnaire-based study was conducted in three regions of Ghana to investigate health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms. When manifesting schistosomiasis-related symptoms or fever, many people try self-medication (usually with allopathic drugs) and a reasonable number do not take action. Overall, about 20% of all urinary and intestinal schistosomiasis-related symptoms were reported to a health facility, which was lower than the 30% for fever. Strikingly, patients with urinary symptoms show very low tendency to seek care compared to fever and to a lesser extent, intestinal symptoms. The rate of health care seeking is lowest for symptoms with chronic characteristics, but when patients take action, they are slightly more likely to report to a health facility. In a multivariate logistic regression analysis, perceived severity consistently showed to be the most important predictor of both health care seeking in general and visiting a health facility for those that take action.

Our findings are consistent with those from our earlier study (Danso-Appiah *et al*. 2004. The proportion of patients not seeking care for urinary symptoms (>60%) is close to what was reported from our earlier study (70%). In both studies the main intestinal symptoms (blood in stool, diarrhoea and abdominal pain) and also fever led to high levels of action, mostly self-medication with allopathic medication. There are some differences in health seeking behaviour variables across the study sites. Generally, people from the south were more likely to take action and visit a health facility than those from central and north. For urinary symptoms, the observed high levels of action cannot be explained from endemicity alone, as the prevalence of infection was similar in the south and central, the north is moderately endemic. The relatively high socio-economic status and high educational level in the south may partly explain the observed difference. Improved knowledge and thus awareness about the consequence of the disease may also have contributed to the difference, as the focus in the south along the Densu Lake has been exposed to increased research activities in recent times compared to the foci in central and north regions. For intestinal schistosomiasis, the difference though may be attributed to the high endemicity of intestinal schistosomiasis in Tomefa, where prevalence of the infection was recorded at >70%. The north is moderately endemic for intestinal schistosomiasis but the central is non-endemic.

Guyatt & Evans (1992) pointed out that in control strategies that rely particularly on passive case detection, the community's perception of the disease is particularly

important in ensuring its effectiveness, since perception influences compliance. The seriousness of schistosomiasis is underestimated at the community level and the tendency to receive treatment from health facilities could be low (Tanner *et al*. 1986; Gazzinelli *et al*. 1998). The findings from our study in which people interviewed perceived the disease as mild-to-moderate is consistent with earlier observations. Stock (1983) examined the impact of distance on the utilization of health care facilities in rural Nigeria and found that utilization declined exponentially with distance. Our results for both sites in the south showed that living far from a health facility promotes any action for chronic symptoms, but not acute symptoms. Strikingly, for hospital/ clinic visit as first action, the results show a consistent trend with people living far visiting a health facility for both acute and chronic cases than those living near a facility. This observation is against the trend of what was expected and cannot be explained from the variables investigated. Higher socio-economic status has been suggested to influence health seeking behaviour and hospital visit (Raso *et al*. 2005; Shaw 2001). In Cote d'Ivoire, Raso *et al*. (2005) found that schoolchildren living in relatively richer households had better access to formal health services than those from poorer homes. The direction of the effect is consistent with what we found in our study, both for any action and hospital visit as first action.

Since our study is based on questionnaires and self-reported symptoms, it is to some extent prone to recall bias and social-desirability bias. In this study, we chose a one-month recall period for our interview and anticipated recall bias especially for mild acute symptoms. However, a study in Ghana investigating the effect of recall on estimation of incidence rate for non-fatal injuries found that one month recall yielded accurate results (Mock *et al*. 1999). Also, many studies measuring acute and chronic disease properties have shown that for a one-month recall period, recall bias is minimal (Keller *et al*. 1997; Balen *et al*. 2007). For schistosomiasis, which presents both acute and chronic characteristics, a careful evaluation concluded that one month recall period is appropriate (Danso-Appiah *et al*. 2004) whilst Van der Werf *et al*. (2003) found no effect of recall period length for blood in urine due to urinary schistosomiasis. Social-desirability might lead to over-reporting of positive practices such as hospital visit. For verification we checked the hospital records that patient keep in their homes. There was good agreement between reported hospital visit and the questionnaire data suggesting that patients did not over report their visits to a health facility. Social-desirability may also have influenced patients' reported opinions about quality of care. However, given the number of people interviewed and the consistent direction of the responses, it is not likely that social-desirability may have affected the results and thus interpretation. We did not study changes in health seeking behaviour over the year. However, it is not likely that seasonal factors

would have affected the validity of the results because schistosomiasis transmission is mostly stable throughout the year in Ghana. Furthermore, occupation in these traditional rural communities hardly changes within the year, and thus availability of money and time to seek health are likely to be stable as well.

The number of cases attending hospital for schistosomiasis-related symptoms (around 20%) seems low if we consider that most people do think that such symptoms are a reason to seek care. However, hospital visit is expected to be selective towards those with heavy infections and that the 20% that visit a health care facility with early symptoms may represent most of those at risk of developing severe long term consequences of the disease. Our data show that the vast majority of patients who seek health care or visit a health facility do so when they perceive the symptom as severe. Hewlett and Cline (1997) observed severity of symptoms as an important determinant for passive case reporting to the clinic for urinary schistosomiasis symptoms. A study in a village in Cameroon showed selective hospital visit for haematuria by high intensity cases that formed only 13% of the overall infection in the population (Slootweg *et al*. 1995).

Population treatment programmes focusing on those aged over 5 years leaving infants and preschool children untreated raises serious concern (Bosompem *et al*. 2004; Odogwu *et al*. 2006; Stothard & Gabrielli 2007). Schistosomiasis often leads to serious complications in infants and preschool children in the form of nutritional deficiencies, retarded growth, reduced physical activity, and impaired cognitive function (Jukes *et al*. 2002; WHO 2002). The finding that children under 10 years showed the highest tendency to visit a hospital/clinic is good news for the potential of passive case finding to supplement such population treatment programmes. Health education of caretakers of infants and preschool children may further raise awareness about the seriousness of schistosomiasis and promote health care seeking by this vulnerable group. However, in practice it is difficult to put such message through as long as populations at risk remain poor, have low level of education and have to deal with many other diseases and infections (Kloos 1995; Sow *et al*. 2003).

The findings of this study have significant public health and control implications especially given the fact that two thirds of patients with urinary symptoms (blood in urine and painful urination) do not seek health care. If treatment is not provided early enough, schistosomiasis can lead to long-term serious disease (King *et al*. 2005). It is worth noting that the development of severe chronic disease is insidious and many late-stage complications are rarely acknowledged to be due to schistosomiasis because there is no clear link between infection earlier in life and later development of severe disease. Our earlier study revealed that over 90% of those that self-medicated or visited chemical shops for treatment did not receive praziquantel (Danso-Appiah

et al. 2004). At the same time, there was no known traditional medicine for treating schistosomiasis-related symptoms. This raises serious concern as self-medication seems less likely to help in morbidity control of schistosomiasis. However, the high preference for orthodox self-medication is a key potential to explore towards passive case-finding.

The case for passive case finding is now compelling: most parts of Africa where the highest burden of the disease is concentrated did not benefit from the donor-supported vertical control programmes (WHO 1998) and although praziquantel use has increased considerably in sub-Saharan Africa following the launch of the 'Schistosomiasis Control Initiative' in 2003 (Colley *et al*. 2001; WHO 2002; Hagan *et al*. 2004) the coverage is still limited. Passive case finding may have a profound public health impact as schistosomiasis-related symptoms show selective hospital visit toward high intensity cases that are likely to develop long-term severe disease (Slootweg *et al*. 1995). The price of PZQ has fallen enormously (Fenwick *et al.* 2003; Fenwick *et al*. 2006; Doenhoff *et al*. 2008) making it affordable for national health care services to procure the drug and stock it in health facilities.

Recent changes in the health care system in Ghana may also be positive for integrated control by passive case finding. In the 1990s, the system of payment for health care delivery within the formal sector was out of pocket payment ('cash and carry') where a patient was required to make full payment for consultation before treatment was provided (Asenso-Okyere *et al*. 1998). Compared to other debilitating diseases such as malaria, few people will spend money to seek health care for a disease perceived as relatively mild and recurring. However, the Ghana health care delivery system has been undergoing restructuring since the millennium to strengthen the peripheral health facilities where most of these cases are reported. Also a new highly subsidised National Health Insurance Scheme (NHIS) has been introduced after 2005 and adult Ghanaians are to pay a monthly minimum subscription of six thousand Ghanaian Cedis (US $0.66). In this regime of payment, the aged, poor and children of parents who both subscribe to the scheme receive free treatment. The scheme is considered the best alternative to the rigid *cash and carry* that pushed health care far beyond the reach of the poor. The rural poor can now receive medical care with a minimum fee.

We conclude that perceived severity of the disease is the most important determinant of visiting a hospital or clinic in Ghana for schistosomiasis-related symptoms. All other factors considered played a negligible or inconsistent role. Schistosomiasis control by passive case-finding within the regular health care delivery looks promising, but the number not visiting a health facility is large and calls for supplementary control options.

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Chapter 7

Quantitative evaluation of integrated schistosomiasis control: the example of passive case finding in Ghana

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7.1 Abstract

Passive case finding based on adequate diagnosis and treatment of symptomatic individuals with praziquantel by the health care facilities is a minimum requirement for integrated schistosomiasis control. Two field studies were conducted in Ghana to obtain quantifications about the steps in this process: (1) a study of health-seeking behaviour through interview of individuals with reported schistosomiasis-related symptoms; (2) a study of the performance of the Ghanaian health system with regard to schistosomiasis case management by presenting clinical scenarios to health workers and collecting information about availability of praziquantel. It appeared that cases of blood in urine (the most typical symptom of *Schistosoma haematobium*) and blood in stool (the most typical symptom of *S. mansoni*) have a very small probability of receiving praziquantel (4.4% and 1.4%, respectively) from health facilities. Programmes aimed at making the drug available at all levels of the health care delivery system and encouraging health-seeking behaviour through health education are not likely to increase these probabilities beyond 30%. This is because many cases with blood in urine do not consider it serious enough to seek health care, and blood in stool usually requires (imperfect) diagnostic testing and referral. We therefore conclude that additional control activities, especially for high-risk groups, will remain necessary.

7.2 Introduction

Over the past decades, control of urinary and intestinal schistosomiasis was mainly based on vertical programmes, co-ordinated and organized at the national level and usually supported by donor organizations (e.g. El Malatawy *et al.* 1992; Barakat *et al.* 1995). The aim was to reduce transmission and infection in populations to levels at least low enough to minimize the risk of serious morbidity. As a result of the relatively high cost of praziquantel, screen-and-treat campaigns (selective population chemotherapy) were considered the most cost-effective strategy in most endemic countries (World Health Organization 1985). However, the long-term results were often disappointing because of rapid re-infection and the expensive nature of these programmes that make them unsustainable after withdrawal of external funding (Gryseels 1989; Kumar & Gryseels 1994).

In 1993, the WHO Expert Committee called for a more prominent role of the regular Primary Health Care System (WHO 1993). Building blocks for this integrated control were defined as health education, diagnosis and treatment, promotion of safe water supply, sanitation and snail control. It was, however, emphasized that the first essential component should be adequate clinical care for patients presenting at a health post or clinic with early signs and symptoms (passive case finding). In any case, this is the only option in countries without any form of organized schistosomiasis control (Engels *et al.* 2002). As pathology is strongly related to intensity and duration of infection, treating early cases may also prevent most of the severe morbidity later (WHO 2002). Moreover, such treatment meets the demands of the populations and strengthens the health system as a whole. The recent resolution of the 54th World Health Assembly (WHA 54.19, 22 May 2001) and the WHO Expert Committee on schistosomiasis and soil-transmitted helminthiasis (WHO 2002) call for a comprehensive approach and recommend ensured access to treatment in primary health care services, associated with regular delivery of treatment to high-risk groups, particularly school-age children, and implementation of plans for basic sanitation and safe water supplies.

The prerequisites for the success of integrated schistosomiasis control through passive case finding are adequate health-seeking behaviour, good access to functional health care facilities, proper treatment and referral strategies and availability of praziquantel. In a multidisciplinary research programme, we have tried to obtain quantifications for each of these steps (Figure 7.1) by conducting field studies in West Africa. This paper aggregates our major findings for Ghana, a country currently restructuring its health care delivery system by shifting responsibilities to peripheral health facilities, with integration of control of parasitic diseases –

including schistosomiasis – in the regular health services and active community participation as central components. We apply the quantifications from our study to estimate the probability that individuals with schistosomiasis-related symptoms receive praziquantel from the Ghanaian health system, and we explore the impact of improvements on this process.

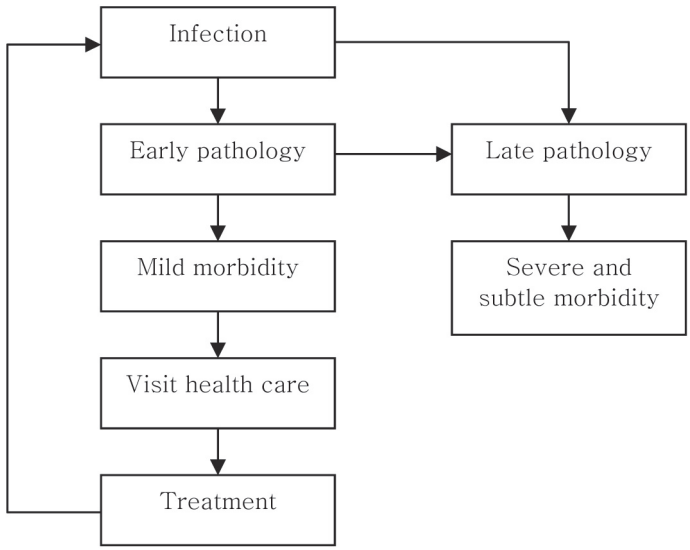

Figure 7.1 Schematic representation of prevention of schistosomiasis morbidity by treatment of cases reporting with mild symptoms.

7.3 Methods

The data for this study were based on two field studies reported elsewhere: one about health-seeking behaviour of individuals with schistosomiasis-related symptoms and the other about functioning of the health system with regard to schistosomiasis control. A brief description of each study is given below.

A questionnaire-based study was conducted in Kokoetsekope (Greater Accra Region, Ghana) from July to September 2000. This rural village is located along the Densu Lake and has about 380 inhabitants, most of them with no or only basic, elementary education. A preliminary survey by the Noguchi Memorial Institute for

Medical Research involving a random sample of a small portion of the population resulted in prevalences of *Schistosoma haematobium* (by urine filtration) and *S. mansoni* (by Kato-Katz faecal smear) of 70% and 78%, respectively. In Kasoa, a nearby commercial town about 2 km away, two health centres and 11 private clinics were available for conventional medical treatment. The health centres are government owned and manned by medical assistants. Patients were required to make full payment for consultation and laboratory investigation (according to the *cash and carry* system) before treatment was provided. The private clinics were headed by either medical doctors or nurses. All inhabitants were interviewed, and for those younger than 6 years or who could not answer the questions themselves, a parent or guardian responded for them. They were asked if they had experienced any of seven schistosomiasis-related signs and symptoms (blood in urine, painful urination, diarrhoea, blood in stool, swollen abdomen, abdominal pain, fatigue) and fever within 1 month before the day of interview. Individuals who reported a sign/symptom were asked what action was taken and whether this included a visit to a health care facility (health centre or clinic). In case they had not visited a health care facility for the reported sign/symptom, they were asked why not. In the present study, we mainly focussed on the results reported for the symptoms blood in urine and blood in stool (including bloody diarrhoea). More details of this study and results for other signs/symptoms can be found in Danso-Appiah *et al.* (2004).

In April and May 2000, a random sample of 70 health care facilities (12 hospitals, 53 health centres and mission clinics, and five private clinics) in four geographically different areas of Ghana were visited. The person in charge of the health facility was interviewed without revealing our specific aim of evaluating schistosomiasis control. We started by presenting four clinical scenarios with symptoms related to schistosomiasis and asked the respondents to explain their usual case management policy for such patients. We wanted to find out if symptom-based treatment was performed, if diagnostic testing was requested and if there was referral for a diagnostic test or treatment. We further asked what the action would be after a positive (i.e. identification of *Schistosoma* eggs) and a negative test, and which treatment would be prescribed. Thereafter, we revealed the focus of our study and asked whether *S. haematobium* or *S. mansoni* infection were present in the coverage area. Respondents from areas with reported schistosomiasis were interviewed using a structured questionnaire about their knowledge of schistosomiasis symptoms and availability and costs of diagnostic tests and praziquantel. In the present study, we used the results for both clinical scenarios most distinctive for urinary and intestinal schistosomiasis, respectively: a 10-year-old girl with blood in urine, without any other signs and symptoms; and a 10-year-old boy with abdominal discomfort and bloody diarrhoea without any other signs and symptoms.

Probabilities of receiving a prescription of praziquantel were calculated from all situations where praziquantel was prescribed directly, after positive diagnostic testing (assuming a 50% chance of a positive result), or after referral of patients to hospitals (using the average management policy of all hospitals in the study, and assuming that all patients will comply with referral and buy praziquantel). The 50% chance of a positive result was based on literature review and appeared a reasonable estimate for both the proportion of patients with blood in urine showing *S. haematobium* eggs in a standard urine centrifugation test, and the proportion of patients with blood in stool showing *S. mansoni* eggs in a standard direct smear test (other, more sensitive tests were not reported; see Van der Werf *et al.* 2003, 2004, for more details and results of this field study).

7.4 Results

There were 318 inhabitants of Kokoetsekope present at the time of the study and only one refused to participate. Using a 1-month recall period, 64 individuals reported blood in urine and 19 (30%) of them reported to have taken action. Nine (47%) of the 19 cases visited a health care facility as first action. Blood in stool was reported by 82 individuals, of whom 48 (59%) took action, among which 12 (25%) visited a health centre or clinic as first option. Another action mostly taken was self-medication, with allopathic drugs four to five times more often used than herbal treatment. The overall proportion of cases visiting a health care facility (about 14% for both symptoms) was lower than for fever (30%) and slightly lower than the average for the other schistosomiasis-related signs/symptoms (about 20%). Overall, teenagers (10-19 years) with schistosomiasis-related symptoms showed a significantly lower tendency to visit a clinic or health centre than children and adults (9%*vs.* 21%).

All 70 selected health care facilities agreed to participate in our study. Interviews of the persons in charge revealed that clinical scenarios comparable to the one about blood in urine have a chance of 66% to receive a prescription of praziquantel, whereas this was 13% for the scenario about blood in stool. For both scenarios, prescription was usually made after diagnostic test (assuming 50% chance of positive result) or it was made in a hospital in case of a referral. The low probability of receiving praziquantel for the second scenario was largely because schistosomiasis was rarely considered as the most likely initial diagnosis (3% when compared with 91% for the first scenario). The proportions of health facilities among those prescribing praziquantel that had it in stock were 47% and 74% for the first and second scenario, respectively. The difference is mainly due to the fact that hospitals (which usually

have praziquantel in stock) constitute the largest part of the few health facilities that prescribe praziquantel in case of blood in stool.

Table 7.1 summarizes the successive steps between having blood in urine or blood in stool and receiving praziquantel, using above quantifications. The overall probability to receive praziquantel from the health system is 4.4% for cases with blood in urine and 1.4% for cases with blood in stool.

Table 7.1 Successive steps in the probability to receive praziquantel for cases with blood in urine and blood in stool

Step	Blood in urine (%)	Blood in stool (%)
1. Proportion seeking health care	30	59
2. Proportion visiting a clinic or health centre out of those seeking health care	47	25
3. Probability of receiving a praziquantel prescription	66	13
4. Proportion of health care facilities having praziquantel in stock of those prescribing it	47	74
Overall probability	4.4	1.4

Proportion seeking health care and visiting a clinic or health centre were based on 64 (of 317 interviewed) individuals in the village of Kokoetsekope (Greater Accra Region, Ghana) who reported blood in urine and 82 individuals who reported blood in stool (including bloody diarrhoea) within one month before the day of interview. Probability of health care facilities prescribing praziquantel and proportion having it in stock were based on interview of health workers in a random sample of 70 health care facilities in different geographical regions of Ghana.

7.5 Discussion

The process of passive case finding as an essential part of integrated disease control has been investigated before, but mainly in a qualitative way. The TB model by Waaler and Piot (1969) is the best known example. To our knowledge, we are the first to have conducted field studies within one country to obtain quantitative information about the steps from perceived symptoms to receiving proper treatment. Although schistosomiasis seems a classical example for integrated disease control (WHO 1993), our study revealed a rather disappointing result for passive case finding in Ghana, with an overall probability of <5% cases with blood in urine or blood in stool receiving praziquantel from the health system. The main bottleneck for blood

in urine is the low tendency of symptomatic cases to seek health care. For blood in stool, and probably other symptoms caused by *S. mansoni*, the bottleneck is the low alertness of health workers about intestinal schistosomiasis, leading to a limited chance of prescribing praziquantel. The overall probability of receiving praziquantel (within or outside the health system) is slightly higher as the drug can sometimes be obtained from privately owned chemical shops (Danso-Appiah *et al.* 2004).

We believe that our measurements and calculations give a realistic picture of the situation in Ghana. Our study on health-seeking behaviour of subjects with schistosomiasis-related signs and symptoms was only a pilot study and constituted a relatively small community. However, preliminary analysis of data from a similar study in Ghana involving big samples of individuals from three locations of varying cultures and ethnicities did not show results markedly different from those presented here. Our study of the performance of health care facilities concerned a representative sample of endemic areas in Ghana, and the main results did not differ between the four regions visited. There was no particular reason for the interviewed health workers to give socially desirable answers, as our interest in schistosomiasis case management was revealed only after the clinical scenarios were presented. Also, the reported presence of praziquantel was cross-checked by the interviewer. Finally, both studies were characterized by a participation rate of nearly 100%.

It is striking that all four steps in Table 7.1 contribute to the low overall probability of receiving adequate treatment. This means that interventions aimed at improving only one step will not have a substantial effect on the overall outcome. Thus, interventions that have effect on multiple steps are necessary.

In this respect, making praziquantel available at all levels of the health system is the most logical option for improvement. Apart from a maximum availability of the drug (step 4), it may increase the probability of prescription (step 3). First of all, there seems more reason to prescribe the drug if it is directly available from the health care facility visited. In Mali, another country where the performance of the health care facilities with respect to schistosomiasis was investigated by our research team (Landouré*et al.* 2003), 85% of the respondents reported to prescribe praziquantel in case of blood in urine, mostly without diagnostic testing or referral (Van der Werf *et al.* 2004). The same study showed that a case with blood in stool in Mali still has a small chance to receive a prescription of praziquantel (19%), although 81% of all health centres had the drug in stock and most health workers knew this symptom of *S. mansoni*. This large difference is mainly due to difficulties in diagnosis of *S. mansoni* infection. Most health workers mentioned other diseases such as bacterial infection and amoebiasis when asked for the first diagnosis of a patient reporting with blood in stool, which may – from a public health point of view – very well be the

best strategy based on the presence of other infections relative to *S. mansoni*. Only in the recent focus of Northern Senegal, with extreme levels of *S. mansoni* infection, diagnostic algorithms were developed and applied to prescribe praziquantel based on symptoms only (Van der Werf *et al.* 2002). In moderately endemic situations, some diagnostic testing will always be necessary. As most Ghanaian health centres and clinics at the peripheral level have no laboratory facilities, this is only possible at the hospital level. As a consequence, this entails the risk of loss of patients due to extra cost (diagnosis, travel, etc.) and time lost.

Availability of praziquantel may also increase the willingness of symptomatic cases to visit a health care facility (step 2). However, it is interesting to note that very few symptomatic cases expressed a negative attitude towards health care (4% reported 'drugs do not help') when asked about the reason for not going to a health centre or clinic (Danso-Appiah *et al.* 2004). Financial reasons ('do not have the money') and perceived severity of the disease ('not serious enough') appeared to be much more important (47% and 44%, respectively). A reduction of the cost of treatment may further increase the tendency to visit a health care facility, but it is not likely to attract the entire 47% as the cost of travel and the loss of income due to time lost (half a day to one day) in seeking hospital care will remain unchanged. Finally, socioeconomic status did not have any effect on the tendency to seek health care, except for the reported reason for not going to a health care facility (Danso-Appiah *et al.* 2004).

The steps in Table 7.1 can now be used to explore what would happen in an ideal situation of wide availability of cheap praziquantel (say 90% of health centres/clinics and 100% of hospitals) and training of health personnel about when to prescribe it. A policy of direct treatment for all cases reporting with blood in urine, assuming a small increase in visiting of health facilities, would lead to an overall probability of receiving praziquantel equal to 16% (step 1 × step 2 × step 3 × step 4 = 30%× 60% × 100%× 90%). A policy to first refer all reporting cases with blood in stool for diagnosis with Kato-Katz (about 70% sensitivity), assuming a small increase in visiting of health facilities but a 30% loss of patients due to referral, will lead to an overall probability of about 9% (59% × 30% × 50% × 100%). These probabilities are four to six times the original values, but still rather low.

Health education can further increase the probability of receiving praziquantel. It may raise awareness in the population about schistosomiasis-related symptoms (step 1), and also encourage symptomatic cases to go to their local health centre or clinic for proper treatment (step 2). In practice, however, it is difficult to put such messages through as long as populations at risk of schistosomiasis remain poor and have to deal with so many other infections. A study in Northern

Senegal showed that even 7 years of health education as part of intense control and research activities were not enough to make more than half of the population accurately quoting symptoms associated with intestinal schistosomiasis (Sow *et al.* 2003). Also, it will not be easy to change local attitudes and perceptions that have evolved over centuries of living with schistosomes: blood in urine is considered a fact of life in many areas endemic for urinary schistosomiasis and sometimes even seen as a sign of maturity (Asenso-Okyere *et al.* 1998). It is not likely that the number of cases seeking health care will change much, but health education may substantially increase the proportion of those that will go to the regular health care (say to 80%). The overall probability to receive praziquantel for cases with blood in urine will then be 29% (40% × 80% × 100% × 90%). For blood in stool, this is 26% (65% × 80% × 50% × 100%).

Thus programmes aimed at making praziquantel available at all levels of health care and encouraging health care seeking by health education are not likely to increase the probability of symptomatic cases receiving adequate treatment beyond 30%. This is because the most common mild symptoms (in particular blood in urine) are often not considered serious enough to seek health care, and blood in stool usually requires (imperfect) diagnostic testing and referral to specialized centres with the risk of loss of patients. A substantial number of cases with mild symptoms will therefore remain untreated with the risk of developing severe morbidity.

With respect to the recent WHO recommendations for schistosomiasis control, we can safely conclude that the current poor availability of praziquantel in health facilities (our study), together with the limited presence of other control measures (mainly confined to Volta Region), poses considerable challenges to the Ghanaian health system. To meet the specific WHO target for all Member States in endemic areas 'of attaining a minimum target of regular administration of chemotherapy to at least 75% and up to 100% of all school-age children at risk of morbidity by 2010' (World Health Organization 2002) will require huge efforts. Our conclusion that even with maximum access to praziquantel about 70% of episodes with blood in urine or blood in stool will be left untreated, demonstrates that integrated control by passive case finding cannot be the only component of successful morbidity control in endemic communities. This confirms current WHO policy that ensured access to treatment in primary health care services should always be complemented by other control activities, notably regular treatment of high-risk groups.

The current study presents a simple but unique approach to provide real-life quantifications to the process of health care integrated schistosomiasis control. Within the framework of the multidisciplinary research programme (illustrated in Figure 7.1) of which this study is part, we aim at conducting further research to

elucidate the overall impact of treatment on reduction of schistosomiasis morbidity. For example, it is interesting to find out to which extent even occasional periods of reduced intensity of infection for those who received treatment after self-reporting with mild systems to the health system will regress, or at least halt, the development of severe pathology and morbidity. It can be imagined that passive case finding selects those with the highest risk. Similarly, more subtle consequences such as growth retardation and impaired cognitive development may be prevented by such occasional treatment of episodes with mild symptoms (Nokes & Bundy 1994). A final judgment of the consequences of integrated control by passive case finding or other treatment approaches can only be obtained after lengthy and costly cohort studies (e.g. Hatz *et al.* 1998). Simulation models aggregating our quantifications on health care seeking behaviour and functioning of health systems with respect to schistosomiasis control, together with an appropriate representation of the dynamics of progression and regression of pathology and morbidity, may be a good alternative.

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Chapter 8

General discussion

8.1 Answering the research questions

In this thesis I have investigated treatment effects of antischistosomal drugs, and explored the strengths and weaknesses of integrating morbidity control of schistosomiasis within the regular health services in Ghana. The studies deepen the understanding of the dynamics of schistosomiasis, and help in identifying effective control strategies for implementation in sub-Saharan Africa. Below, I have outlined how the five research questions formulated in Section 1.7 of the general introduction were answered in the preceding chapters (Section 8.1). Also, I will discuss the implications of our studies for monitoring and evaluating schistosomiasis control (Section 8.2), impact of population treatment on transmission of the infection (Section 8.3), options for control (Section 8.4), and list the main conclusions and recommendations (Section 8.5).

Research question 1: Is there evidence of resistance against praziquantel for Schistosoma mansoni infection?

Current evidence indicates that resistance against praziquantel is unlikely, but its possibility cannot be ruled out entirely.

In our meta-analysis in which we compare praziquantel cure rates from different countries, we demonstrated that the low cure rates in Senegal could largely be explained by the high intensity of infection before treatment, together with the relatively sensitive diagnostic techniques used (Chapter 2). However, after correcting for pre-control intensity and sensitivity of diagnosis, the cure rates from Senegal are still somewhat lower than expected, so that we cannot fully reject the possibility of resistance.

After the publication of this evidence in 2002, various field and laboratory studies have been conducted to assess the effects of praziquantel but none associated the low cure rate to resistance (Kabatereine *et al.* 2003; Cioli *et al*. 2008). A recent robust Cochrane systematic review assessing efficacy of drugs for treating urinary schistosomiasis documented an association between high endemicities and poor cure rates for praziquantel and other antischistosomal drugs but did not identify evidence of clinical resistance against PZQ (Chapter 3). Nevertheless, the impending danger of praziquantel resistance and the need for continued monitoring has been re-emphasised in Chapter 3 and elsewhere (Cioli *et al*. 2008).

Our study provides evidence that lack of quantitative evaluation and precise interpretation of research data led to the speculation about emergence of resistance

against praziquantel. Although our data could not rule out resistance completely, we demonstrated that this is less likely. Nevertheless, field treatment studies should be monitored with the appropriate surveillance tools in order to identify early warning signs, which will allow an unequivocal distinction between drug failure and normal drug performance. A user-friendly chart that can be used to monitor PZQ clinical resistance has been developed from the confidence limits of effect estimates obtained from our meta-analysis to assist field researchers determine whether future low cure rates deviate from expected (Chapter 8.2).

Research question 2: What is the potential of antischistosomal drugs other than praziquantel for treating urinary schistosomiasis?

Metrifonate is effective against urinary schistosomiasis. Evidence on the artemisinins is inconclusive. Combination therapies should be tested in randomized controlled trials.

This research question was answered by a systematic review of 24 Randomized Controlled Trials (RCTs) that together involved 6,315 participants (Chapter 3). There appeared to be no difference in effect between metrifonate (10 mg/kg) given every four months for one year and the standard dose of praziquantel (40 mg/kg), but this may not be conclusive as the evidence came from only one trial (King *et al*. 1988). Metrifonate (10 mg/kg 3 times at 14-day intervals) showed similar effect to praziquantel (30 mg/kg). However, a key problem with metrifonate is that public health programmes often recommend multiple-dose regimens such as 3 doses of 7.5 to 10 mg/kg administered once every 14 days or every 4 months, which are difficult to implement and might compromise compliance.

Research carried out over the past 15 years revealed the antischistosomal properties of artemisinin derivatives (artesunate and artemether), which act especially on the young developing stages of the parasites (Utzinger *et al.* 2007), while praziquantel acts against the adult worms and the very young schistosomula (Sabah *et al.* 1986). However, a recent trial showed that artesunate was not effective against *S. haematobium* infections (Borrmann *et al.* 2001). Combining artesunate and the standard dose of praziquantel did not improve efficacy over praziquantel alone.

Amoscanate is a broad-spectrum anthelminthic drug that exhibits activity against all major human schistosome parasites (Striebel *et al.* 1976), and also against other systemic parasites (e.g. filariae) and gastrointestinal nematodes (e.g. hookworms). The drug was tested extensively in China (Bueding 1976; Striebel *et al.* 1976). Mutagenic

metabolites were detected in urine of mammals given this drug (Batzinger *et al.* 1977). It has been abandoned because of concerns over liver toxicity. Nonetheless, experts have suggested that amoscanate may represent a unique, broad-spectrum schistosomicide with the appropriate structural modifications to decrease liver toxicity (Cioli *et al.* 1995). Recent studies in Egypt investigating the efficacy of myrrh (Mirazid) gave poor results (Barakat *et al.* 2005; Botros *et al.* 2005).

Most drugs for treating urinary schistosomiasis have been abandoned because of poor effect or adverse events and current treatment options are limited to praziquantel. Given similar efficacy profiles between metrifonate and praziquantel from this review, we suggest metrifonate be reinstated on the WHO Model List of Essential Medicines as second-line treatment for urinary schistosomiasis to ease the drug pressure on praziquantel.

Research question 3: What are the methodological limitations in schistosomiasis control?

Many trials were underpowered, had inadequate allocation concealment, suffered from loss to follow-up and lacked standardized definitions. New schistosomiasis trials must keep to contemporary standards of clinical research.

The validity of RCTs rests in part on adequate allocation concealment and minimal losses to follow-up, and weaknesses in both these aspects were found in the trials included in the current meta-analysis. Without adequate allocation concealment properly developed random allocation sequences can be subverted (Schulz and Grimes, 2002). A likely explanation for only four trials (17%) included in our final analyses adequately concealing allocation is that this was not particularly relevant an issue at the time the trials were implemented some 2-3 decades ago. Even after the publication of the CONSORT statement (Begg *et al.* 1996) and despite continued educational efforts, the quality of reporting of RCTs still needs improvement (Altman *et al.* 2001; Moher *et al*. 2001).

The effect of losing patients during follow-up is crucial as this relates to the internal validity of the trial. In our systematic review (Chapter 3), we could not do a sensitivity analysis to evaluate the effect of loss to follow-up because data were not sufficient. We encourage trialists to take particular note of this issue and ensure that losses during follow-up are minimised and power is preserved in future trials. Also, sensitivity of diagnosis can impact strongly on observed cure rates as clearly shown for both *S. mansoni* (de Vlas and Gryseels 1992; Booth *et al.* 2003) and *S. haematobium* (N'Goran *et al.* 2003). Sensitivity will affect in particular the detection of light infections during follow-up. The considerable variation in diagnostic criteria may be explained

by the fact that the WHO classification as light (1-49 eggs/10 ml urine) and heavy infection intensity (≥50 eggs/10 ml urine) was endorsed only recently (WHO, 2002). Because of the different thresholds used, it was not possible to combine and analyse the heavy infections data, which is an important outcome measure, particularly in view of morbidity control being the current mainstay of schistosomiasis control.

The age of participants enrolled in RCTs may also influence results. Here, 22 trials out of 24 recruited school-aged children. Hence the overall effect estimates as reported in this review may be lower than studies including all-age subjects, as adults are known to respond better to treatment (WHO, 2002). However, restricting treatment to school-aged children alone leaves untreated adults still excreting eggs to maintain transmission, if indeed transmission is a function of egg output. This brings us to two important sets of considerations. First, data should be reported separately for children and adults before, if necessary, pooling the data to assess overall effects. Second, the purpose of studies depends on the target population. Studies in children are more apt to assess the 'true' efficacy of a drug, while whole-population studies are more suited to assess the programmatic effectiveness and effects on control of interventions.

Research question 4: What are the determinants of health care seeking behaviour for schistosomiasis-related symptoms in Ghana?

Only perceived severity of symptoms consistently predicted tendency to seek health care.

Our studies in Ghana revealed three main health care seeking practices namely: "Doing nothing", "Self-medicating" and "Visiting a health facility" (Chapter 5 & 6). The large majority (about 60%) with blood in urine did not seek health care, whereas those seeking care for diarrhoea, abdominal pain and fever mostly engaged in self-medication with allopathic medication. In a multivariate logistic regression analysis, perceived severity was the only factor consistently predicting health care seeking for all seven symptoms, including fever for malaria, whereas geographic location did not have a clear impact. On average 20% of schistosomiasis-related symptoms were reported to health facilities (hospitals or clinics), with slightly higher rate for fever (around 30%).

Unlike urinary symptoms, intestinal symptoms including diarrhea, blood in stool and abdominal pain, and also fever led to high levels of health care action, but mostly self-medication with allopathic medication. Among those self-medicating, over 90% that visited chemical shops did not receive Praziquantel and there was no known

herbal treatment for schistosomiasis (Chapter 5). The public health implications are grave as self-medication seems less likely to help in morbidity control of schistosomiasis. However, the high preference for orthodox medication compared to other remedies is a key potential worth exploring to increase the utilization of the regular health system.

Our data showed that the vast majority of patients would seek health care or visit a health facility when they perceive the symptom as severe or serious. Hewlett and Cline (1997) observed severity of symptoms as an important determinant for visiting a clinic for urinary schistosomiasis symptoms. A recent systematic review identified severity of symptoms as a key determinant of hospital visit (Shaikh and Hatcher 2007). Guyatt and Evans (1992) pointed out that in control strategies that rely particualrly on passive case detection, the community's perception of the disease is particularly important in ensuring its effectiveness, since perception influences compliance. Given that over 60% of individuals interviewed consider schistosomiasis not as a serious disease is a potential setback, and may also explain the low hospital turn out rate. However, fever, a term loosely used to refer to malaria in Ghana which is commonly perceived as a serious disease (Agyepong 1992; Asenso-Okyere and Dzator 1997) showed that <30% visited a hospital suggesting that the number of cases visiting health facilities for schistosomiasis-related symptoms may after all not be as bad.

Research question 5: What are the strengths and weaknesses of integrating morbidity control of schistosomiasis within the regular health services in Ghana?

Passive case finding remains the most effective and sustainable schistosomiasis control strategy in Ghana. Because of the large numbers not visiting health facilities, passive case finding should be supplemented with other control measures such as school health programmes and community directed treatment.

From our field studies in Ghana, we obtained quantifications about the steps in integrated schistosomiasis control by passive case-finding within the regular health system (Chapter 7). Our study revealed an overall probability of <5% cases with blood in urine or blood in stool receiving praziquantel from the health system. The main bottleneck for blood in urine is the low tendency of symptomatic cases to seek health care (Chapter 5 & 6). For blood in stool, the bottleneck is the low specificity that makes it less easy for clinical diagnosis by health workers and thus leading to a limited chance of prescribing praziquantel. This is less encouraging for passive case finding within the regular health care delivery system in Ghana.

It is striking that all four steps as outlined in Table 7.1 (Chapter 7) contributed to the low overall probability of receiving adequate treatment. This means that interventions aimed at improving only one step will not have a substantial effect on the overall outcome. Thus, interventions that have effect on multiple steps may be necessary for effective control. In this respect, making praziquantel available at all levels of the health system is the most logical option for improvement. Apart from a maximum availability of the drug, it may increase the probability of prescription. This is reasonable to prescribe the drug if it is available from the health care facility visited. In Mali, another country where the performance of the health care facilities with respect to schistosomiasis was investigated by our research team (Landouré *et a*l. 2003), 85% of the health care providers reported to prescribe praziquantel in case of blood in urine, mostly without diagnostic testing or referral (Van der Werf *et al*. 2004). The same study showed that a case with blood in stool in Mali still has a small chance to receive a prescription of praziquantel (19%), although 81% of all health centres had the drug in stock and most health workers knew this symptom of *S. mansoni*. This difference may be due to difficulties in diagnosing *S. mansoni* infection on the basis of clinical presentation.

The questionnaire-based interview of health care providers about diagnosis and management of hypothetical schistosomiasis-related signs and symptoms revealed that health workers mentioned diseases such as bacterial infection and amoebiasis when asked to rank their diagnosis of a patient reporting with blood in stool (Van der Werf *et al.* 2003). This suggests that in moderately endemic situations, some diagnostic testing may be necessary. However, most Ghanaian health centres and clinics at the peripheral level have no laboratory facilities. Diagnosis is only possible at the hospital level, but this unlikely to be attractive to patients owing to the extra cost of travel to these referral centres and diagnosis. The good news is that the situation in Ghana has changed and the Ghana health care delivery system has been undergoing restructuring since the millennium to strengthen the peripheral health facilities where most of these schistosomiasis-related symptoms are reported. Also the system of payment for health care within the formal sector 'cash and carry' which required patients to make full payment for consultation before treatment was provided has been replaced with a new highly subsidised National Health Insurance Scheme (NHIS). Within NHIS adult Ghanaians pay a monthly minimum subscription of six thousand Ghanaian Cedis (US $0.66). The aged, poor and children of parents who both subscribe to the scheme receive free treatment. The scheme is considered the best alternative to the rigid *cash and carry* that pushed health care far beyond the reach of the poor and the rural poor can now receive medical care with a minimum fee.

Passive case finding within the regular health care delivery looks promising on the basis of no significant differences in health seeking behaviour for schistosomiasis-related symptoms across Ghana. However, quantifications from our study (Chapter 7) showed that cases of blood in urine and blood in stool have a very small probability of receiving praziquantel treatment (4.4% and 1.4%, respectively) from the regular health facilities. The quantifications also suggest that programmes aimed at making the praziquantel available at all levels of the health care delivery system and encouraging health-seeking behaviour through health education are not likely to increase the probabilities of hospital visit beyond 30%. Therefore, at the moment, we conclude that passive case finding should be pursued, but in addition to School Health Programmes and Community Directed Treatment.

8.2 Monitoring praziquantel resistance

Praziquantel is the only drug for schistosomiasis. In the 1990s unusually low cure rates (18–38%) were reported from Senegal raising fears for emergence of resistance to praziquantel (Stelma *et al*. 1995). Laboratory trials also showed decreased sensitivity to *S. mansoni* strains obtained from Senegal (Bennett *et al*. 1997; Fallon *et al*. 1997). This prompted the European Commission to establish an International Initiative on Praziquantel Use in the late 1990s (Renganathan and Cioli 1998; Kusel and Hagan 1999). The panel of experts reviewed reports of low efficacy of trials from Senegal and Egypt (Stelma *et al*. 1997; Guisse *et al*. 1997). However, they could not distinguish between normal activity and failure of praziquantel. Notwithstanding, the group of EC-Concerted Action on Praziquantel advocated continued monitoring and evaluation of resistance to praziquantel.

Use of praziquantel has increased because of the policy adopted at the 54th World Health Assembly to increase distribution of the drug and treat at least 75% of school-aged children and other high-risk groups living in endemic areas by 2010 (Colley *et al*. 2001; WHO 2002; Hagan *et al.* 2004), and efforts made by the Schistosomiasis Control Initiative to treat millions of school-aged children in selected African countries (Fenwick and Webster 2006).

In Chapter 2, PZQ cure rates (i.e. the proportion testing negative at follow-up) in different endemic settings were studied in a meta-analysis. Because Senegal did not rule out the suspicion about resistance to PZQ (Chapter 2) using the lower confidence limit of the generated estimates from the meta-analysis, we constructed a user-friendly chart to assist field researchers to decide to what extent future low cure rates deviate from expected (see Figure 8.1).

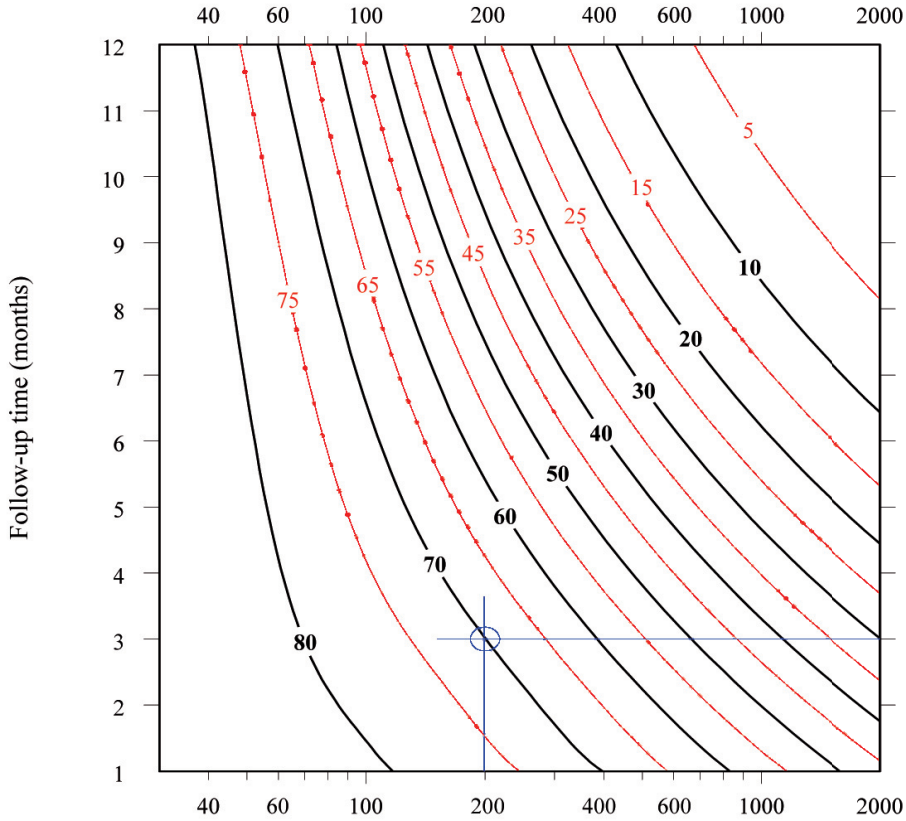

Figure 8.1 Chart to predict normal cure rate by praziquantel. Given a combination of initial intensity of *Schistosoma mansoni* infection (geometric mean epg of positive individuals) and follow-up time (months), the lower limits of expected cure rates for the standard dose of 40 mg/kg PZQ in selective population treatment can be determined from the black and red contour lines. The graph gives the lower limit of the 95% confidence interval. Predictions are only valid for entire communities (or representative sub-samples) and a standard thick smear diagnosis of a single stool specimen. The blue lines illustrate how the cure rate at 3-months follow-up in a community with initial intensity of infection equal to 200 epg can be determined. Where the horizontal and vertical blue lines meet (open circle), the lower limit is estimated from the contour line at 70%. Thus, for this example, cure rates below 70% raise concerns about performance of PZQ and >70% suggests normal effect.

This chart should be used with caution because: (1) the evidence is based only on the standard single dose of 40 mg/kg praziquantel and (2) data from Senegal deviated from data coming from other locations. We hope to update the review and chart with new data, and we will assess the impact of excluding the data from Senegal. Nevertheless, this chart can still be used because the data from Senegal were small compared to data coming from other countries used in creating this chart.

8.3 Impact of population treatment on transmission

For years scientists have been baffled with the transmission dynamics of schistosomiasis. Field studies show that prevalence of infection returns to pre-control levels within a few months following population treatment (Sukwa *et al.* 1988; Gryseels *et al.* 1991; El Malatawy *et al.* 1992; Ernould *et al.* 1999; Kabatereine *et al*., 2003; Satayathum *et al*., 2006). Apparently, the substantial reduction in worm burden and sustained decrease in egg output resulting from such programmes do not lead to diminished force of transmission of the infection although many researchers share the view of the indirect effect of reduction in population egg output on transmission (Woolhouse *et al.* 1998; Vercruysse *et al.* 2001).

There are not many good studies on schistosome transmission, and dynamic models have been used to predict the impact of population chemotherapy programmes on transmission through the monitoring of changes in the parasite population after treatment (Medley and Bundy 1996; Guyatt *et al.* 1993; Chan *et al.* 1994). The assumption in most of these models is that the number of worms an individual harbours has a direct bearing on his contribution to the overall transmission within the population. Also, there is an overdispersed distribution of infection in the population with most infected individuals carrying light infection while only a few harbour very heavy infection (Bensted-Smith *et al.* 1987; Chandiwana and Taylor 1990; Utzinger *et al.* 2000). Transmission is fuelled mainly by this core fraction of high 'transmitters' (Woolhouse *et al.* 1998). Thus, it has been assumed that treatment programmes targeted to 20% of the high egg excreters responsible for the vast majority of egg excretion in the population that is thought to reach the transmission sites will lead to a reduction of transmission by at least 80% (Woolhouse *et al.* 1998). However, in the targeted chemotherapy approach aimed at treating high egg excreters, no impact on transmission was achieved (Ouma *et al.* 1985; Polderman *et al.* 1989; Butterworth *et al.* 1991).

Explanation of the dynamics of schistosome transmission after population treatment needs data from cercariometry but such data are difficult to come by

and are mostly unavailable. Fortunately, a unique opportunity has been provided to test the effect of chemotherapy on transmission by using datasets from a big control programme by Barakat *et al.* (1995) that used two approaches of population chemotherapy. The data involved either whole population treatment (screening all inhabitants in a community and treating all positives) or part of the population (screening random samples and treating those found positive). The aim of the study was to test whether transmission of *S. mansoni* infection can be influenced by reducing population egg output. The specific objective was to assess whether cure rates differ between treating 'whole' population versus 'part' of population treated. The assumption is if chemotherapy affects transmission through reduction in population egg output, then higher cure rates should be expected from treatment of a 'whole' community compared to treating only 'part' of the community. Detailed description of the study population and data has been published by Barakat *et al.* (1995).

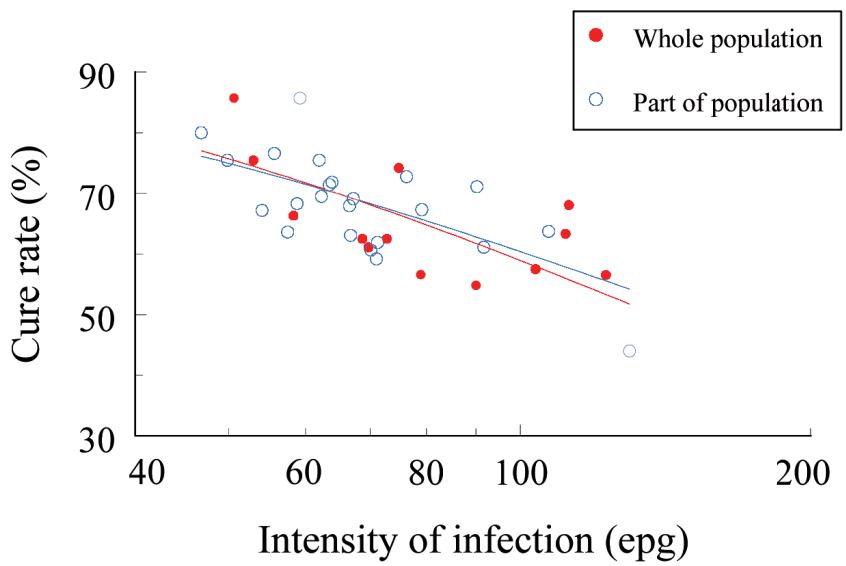

Figure 8.2 The relationship between *Schistosoma mansoni* pre-treatment intensity of infection and cure rate following treatment with the standard 40 mg/kg dose of praziquantel. Intensity of infection (logarithmic scale) is geometric mean of egg count per gramme of faeces (epg) for only positives. Cure rate denotes the percentage of treated subjects who showed no eggs through faecal examination at follow-up. Open circles represent situations where all individuals in a village were screened and positive cases treated (whole population). Closed dots represent treatment of positive cases from screening only random samples (part of population). Data come from Barakat *et al.* (1995).

As clearly demonstrable, there is no apparent difference between cure rates from communities in which only part (random samples) were selected for screening and treatment and that involving entire populations of communities (p = 0.91). This suggests that chemotherapy has no significant impact on schistosome transmission. Figure 8.2 also shows that the higher the pre-control intensity of infection the lower the cure rates. The best fitting regression model equations were: (a) *Logit cure rate* = 4.9-0.97*(*ln epg*) for part of population and (b) *Logit cure rate* = 5.5-1.12*(*ln epg*). A major limitation about this study is that the follow-up of 12 months is long and re-infection is likely to have a high degree of effect on the cure rates.

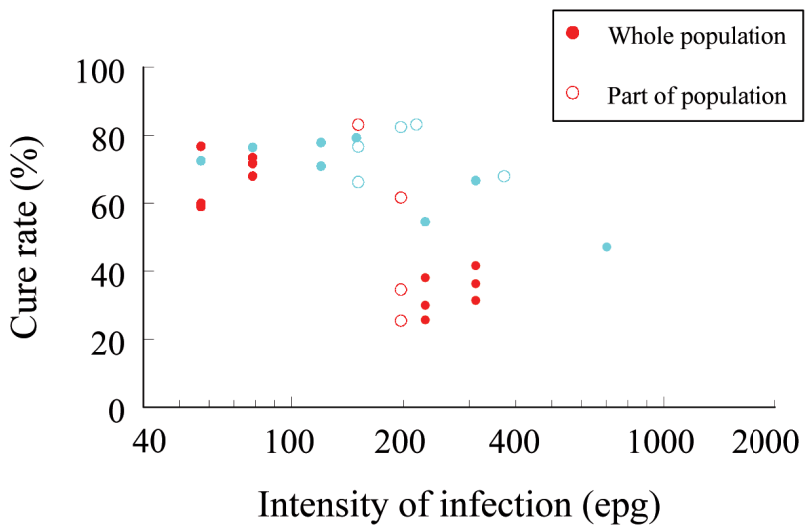

Figure 8.3 The relationship between *Schistosoma mansoni* pre-treatment intensity of infection and cure rate following treatment of children with the standard 40 mg/kg dose of praziquantel after <3 months follow-up (blue) and >9 months follow-up (red). Intensity of infection (logarithmic scale) is geometric mean of egg count per gram of faeces (epg) for only positives. Cure rate denotes the percentage of treated subjects who showed no eggs through faecal examination at follow-up. Open circles represent treatment of positive cases from screening only random samples (part of population). Closed dots represent situations where all individuals in a village were screened and positive cases treated (whole population).

We also did a step-wise search for studies, which included MEDLINE, EMBASE, LILACS, conference proceedings and contacted specialists in the field. We assessed eligibility and methodological quality of the identified trials and the data analysed

with logistic regression models (details of the study can be found in chapter 2). In the current study we restricted our analysis to children living in communities in which 'whole' or 'part' of the population was treated with the standard single dose of PZQ (40 mg/kg). We considered short-term treatment evaluations at less than three months (blue) and over six months folow-up (red).

The higher the pre-control intensity of infection the lower the cure rates. There is no apparent difference between cure rates from communities in which only part (i.e. only the children) were selected for screening and treatment and that involving entire populations of communities (i.e. also adults treated). This again suggests that reinfection was comparable in both groups and that chemotherapy has no significant impact on schistosome transmission.

Thus, in contrast to assumptions in most models, no apparent difference in cure rates was observed between whole and part of population treatment. We believe that a very low threshold allows transmission to go on uninterrupted. This may also explain why even a combination of chemotherapy and intensive snail control hardly prevented infection levels from rapidly returning to pre-treatment values (Saladin *et al.* 1983; Sukwa *et al*. 1988; Farag *et al.* 1993; Wu *et al.* 1993; Li *et al.* 2000).

Our finding has implications for the expected impact of a vaccine with direct effect in only vaccinated individuals. Use of a vaccine is not really different from chemotherapy as protection against the infection is rather low, at best partial (Liu *et al*. 1995; Katz 1999; McManus 2000; Capron *et al.* 2001). Results from preclinical trials in animals have shown antiworm fecundity (Boulanger *et al.* 1995, 1998; Liu *et al.* 1995; Capron *et al.* 2001). Nevertheless, if vaccination can keep egg counts greatly reduced for a longer period of time than chemotherapy, then this would demonstrate a reduction in transmission. In contrast, chemotherapy is considered a one-off event but this does not mean that the effect disappears within a short time. In treated individuals, egg output usually does not return to 50% of the initial value one to two years after treatment. Needless to say that a vaccine with at most 50% reduction in egg output for persons vaccinated has a smaller impact on overall population egg output and transmission than chemotherapy during one year.

Our study provides evidence that transmission of schistosomiasis is not influenced by population interventions such as selective treatment aimed at reducing worm loads and thus egg output. We demonstrated that transmission of schistosomiasis is very efficient. Even a substantial reduction in the population egg output does not lead to a noticeable lowering in the rate of re-infection in the treated individuals. On the basis of this, models that simply assume a linear increase in the rate of transmission with population egg output may be inaccurate. Existing transmission models need to be updated to include a rapidly reaching saturation point where the

force of transmission levels-off (plateau). Existing transmission models need to be updated to include a saturation point where the rate of transmission levels-off.

8.4 Prospects of passive case-finding for schistosomiasis-related symptoms within the regular health care delivery in Ghana based on experiences from health seeking behaviour studies

Most of the people interviewed said they would seek health if they perceive the symptom as severe or serious. However, over 40% of people interviewed think schistosomiasis is not a serious disease. Health education may raise awareness in the population about schistosomiasis-related symptoms, and encourage symptomatic cases to seek care. However, such an approach is difficult in poor communities that have to deal with so many other infections. A study in Northern Senegal showed that even 7 years of health education as part of intense control and research activities were not enough to make more than half of the population accurately quoting symptoms associated with intestinal schistosomiasis (Sow *et al.*2003).

Schistosomiasis in infants and preschool children is a serious public health problem in Ghana (Bosompem *et al.* 2004) and elsewhere (Odogwu *et al.* 2006), but population treatment programmes have focused on those aged over 5 years leaving infants and preschool children untreated (Stothard and Gabrielli, 2007). Schistosomiasis often leads to serious complications in infants and preschool children in the form of nutritional deficiencies, retarded growth, reduced physical activity, and impaired cognitive function (Jukes *et al.,* 2002; WHO 2002). From our study, infants and preschool children showed the highest visit to a health facility than teenagers and adults. Health education of caretakers of infants and preschool children may raise awareness and promote hospital visit by this vulnerable group to receive treatment.

Since the introduction of safe and efficacious drugs in the 1970s and praziquantel in the late 1970s until now, pregnant and lactating women, as well as children under 5 years old have been denied treatment (Johansen *et al*. 2007). In a recent review, the reasons for excluding children were attributed mainly to the following issues (Stothard and Gabrielli 2007): (i) information documenting the safety of praziquantel in this age group is lacking; (ii) PZQ tablets are rejected by children and syrup formulations are not readily available; and (iii) the dose-pole used for determining the dose of praziquantel which is recommended by the WHO and applied in these control

programmes only works from >94 cm in height. Given these operational problems, it has been suggested that the only way these group can benefit from treatment is through the regular health systems and clinics where infected children could get treatment (Stothard and Gabrielli 2007). We believe that health facility-based treatment or case management is the best way to monitor untoward adverse events following treatment. Also, passive case finding may have a profound public health impact as schistosomiasis-related symptoms show selective hospital visit toward high intensity cases that are likely to develop long term severe disease (Slootweg *et al.* 1995). More importantly, most parts of Africa where the highest burden of the disease is concentrated have not benefited from the donor-supported vertical control programmes (WHO 1998). Although praziquantel use has increased considerably especially in countries in Africa selected as part of the 'Schistosomiasis Control Initiative', which was launched in 2003 (Colley *et al.* 2001; WHO 2002; Hagan *et al.* 2004), as with vertical control programmes the SCI is not expected to be sustainable in the long term when donor funds are withdrawn. In 2001, the Joint Meeting of the Expert Committees on the Control of Schistosomiasis and Soil-transmitted Helminths stressed the need for effective and efficient health systems-based control by passive case finding (WHO 2002).

Furthermore, an opportunity has arisen, in that the system of payment for health care delivery within the formal sector - which was out of pocket payment ('cash and carry') where a patient was required to make full payment for consultation before treatment was provided - has changed. The old regime that pushed formal health care from the reach of the poor (Asenso-Okyere *et al.* 1998) has been replaced with a new highly subsidised National Health Insurance Scheme (NHIS) in which adult Ghanaians are to pay a monthly minimum subscription of six thousand Ghanaian Cedis (US $0.66). In this scheme, the aged, very poor and children of parents who both subscribe to the scheme receive free treatment. The rural poor can now receive hospital-based care with a minimum fee. Also the general health system in Ghana has been undergoing restructuring since the millennium to strengthen the peripheral health facilities where most of these cases are reported.

At the moment passive case finding should be complement with School Health Programmes and Community Directed Treatment (ComDT). Massa *et al.* (2009) found villagers in Tanzania preferred a ComDT approach and took the responsibility of selecting the community drug distributors who distribute drugs to the schoolchildren. Their main concern about the school-based approach was that it was limited in reaching the non-enrolled children. A similar study is underway in Ghana in one of our study areas in the north (Chapter 6) and we believe that this may contribute evidence to inform policy in Ghana in the context of integrating schistosomiasis control within the regular health care delivery service.

8.5 Conclusions and recommendations

Conclusions

1. Current evidence indicates that resistance against praziquantel in Senegal is unlikely, but its possibility cannot be ruled out.
2. Both praziquantel and metrifonate are safe and efficacious in the treatment of urinary schistosomiasis.
3. Most schistosomiasis trials are insufficiently powered, lack standardization in assessing and reporting outcomes, and also have other methodological limitations.
4. The health services in Ghana show potential in diagnosing and treating schistosomiasis, but the number of patients visiting a health facility is low.

Recommendations

1. Metrifonate should be reincluded in the WHO model list of essential medicines.
2. New schistosomiasis trials must keep to contemporary standards of clinical research.
3. Passive case finding remains potentially the most effective and sustainable schistosomiasis control strategy in Ghana, but it should be supplemented with additional control options such as school health programmes and community directed treatment.

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Summary

The thesis assessed antischistosomal treatment effects, and explored the possibilities of integrating morbidity control of schistosomiasis within the regular health services of Ghana.

Chapter 1 introduces the schistosomiasis problem, available drugs and treatment effects, control strategies and the research questions addressed in this thesis. Schistosomiasis is a parasitic worm infection of the tropics, characterized by a complex transmission cycle, involving a fresh water snail as intermediate host. In Africa, there is urinary (by *Schistosoma haematobium* worms) and intestinal (by *S. mansoni*) schistosomiasis, and both can be treated by praziquantel, the only widely available drug. Schistosomiasis can present as acute, but mostly as chronic disease. An estimated 780 million people are at risk and more than 200 million are infected with annual burden due to schistosomiasis estimated at 4.5 million disability-adjusted life years (DALYs) of which over 85% is confined to sub-Saharan Africa. Recent reviews however suggest disability weights might be underestimated up to 15 times as previous studies did not consider cause-specific mortality and 'subtle' morbidity in their calculations. The disease is largely related to poverty but efforts to alleviate poverty by creating water-related development projects tend to introduce the disease to new areas or increase transmission of the infection and hence exacerbate the disease burden. Four main control strategies, health education, water supply and sanitation, control of the intermediate host snail and morbidity control have been implemented in the past with mixed successes. The current objective of control is to reduce or eliminate illness through community-based treatment with the standard 40 mg/kg of praziquantel, the only drug currently on the WHO Model List of Essential Medicines for treating all the forms of schistosomiasis. The coverage and distribution of praziquantel have increased enormously following the policy adopted at the 54th World Health Assembly to treat at least 75% of school-aged children and other high-risk groups living in areas with high burden of the disease by 2010. Also new effort made by the Schistosomiasis Control Initiative (SCI) to treat millions of school-aged children in selected countries of Africa has led to a sudden increase of drug pressure on praziquantel. Although speculations about resistance against praziquantel were high, no study provided quantitative evidence or interpretation of the data to distinguish between normal and abnormal treatment effects of praziquantel.

The vertical approach, organized and co-ordinated separately from the regular health service delivery, has been difficult to sustain operationally and financially. This

led to the consideration of integration of control within the regular health services – 'the horizontal approach' – as a more viable option. The World Health Organization Expert Committee and programme managers from endemic countries met in the early 1990 and emphasized that any viable strategy to control schistosomiasis should aim at integrating adequate clinical care for patients consulting the health facility with schistosomiasis-related symptoms (i.e. passive case finding and clinical management). Then, in 2001 the horizontal approach was endorsed by the Joint Meeting of the Expert Committees on the Control of Schistosomiasis and Soil-transmitted Helminths whilst acknowledging the shortfalls of the vertical approach. They called for a comprehensive access to treatment for schistosomiasis cases within the regular health service. However, there was hardly any evidence on whether patients suffering from schistosomiasis-related symptoms visit health facilities and which factors influence their decision to seek health care.

The thesis is made up of two parts. Part I looks at analysis of existing research data to identify knowledge gaps in drug treatment of schistosomiasis with emphasis on praziquantel, and seeks to explore potential alternatives or second-line treatments to praziquantel. Part II involves investigations into determinants of health seeking behaviour for schistosomiasis-related symptoms through field studies in Ghana to determine the potential for integrating control within the regular health service. Related to Part I the following research questions are addressed: (1) Is there evidence of resistance against praziquantel for *S. mansoni* infection; (2) What are the knowledge gaps in the treatment of schistosomiasis; (3) What is the potential of antischistosomal drugs other than praziquantel. Part II addresses the questions: (4) What are the determinants for health care seeking behaviour for schistosomiasis-related symptoms in Ghana; and (5) What are the strengths and weaknesses of integrating morbidity control of schistosomiasis within the regular health services in Ghana?

Chapter 2 focuses on praziquantel for treating *S. mansoni* infections and praziquantel resistance. Selective treatment of *S. mansoni* infections in various endemic countries usually presents cure rates of >70% when using the standard single 40 mg/kg dose. However, unusually low cure rates (18–38%) were reported from Senegal in West Africa, raising fears for emergence of resistance (or tolerance) to praziquantel. Subsequent trials in the same focus also showed cure rates lower than normal, and more worryingly, a normal cure rate with oxamniquine, the alternative drug for *S. mansoni* infection. Although other reports suggested that the low *S. mansoni* cure rates in Senegal could be explained by the high initial intensities of infection, they could not quantify this assumption. A major problem was the precise

quantitative interpretation of cure rates to allow the distinction between drug failure and normal drug performance.

We analysed research data from various locations and the factors that could determine the outcome of population treatment quantified by a meta-analysis. Following a step-wise search of appropriate databases, textbooks and references for published articles, 11 studies (from 1983 to 1999) were suitable for inclusion in the analysis. The objective was to interpret the low cure rates from Senegal on the basis of trends from other studies to determine the true meaning of the reported low cure rate. A combination of models demonstrated that the high pre-treatment levels of infection partly explained the consistently observed low cure rates. We established that even at 95% efficacy, a sufficient number of surviving schistosomes would remain to cause sustained egg excretion in most of the subjects who received treatment given the initial intensity of infection in Senegal, where mean egg-loads were extremely high. We also showed that the relatively sensitive diagnosis applied in Senegal contributed to the seemingly low cure rates. However, after correction for initial intensity and sensitivity of diagnosis, Senegal still showed a slight but statistically significant lower cure rate. We concluded that there is a small likelihood of resistance to praziquantel.

In **Chapter 3** we assessed drugs for treating urinary schistosomiasis. Praziquantel is virtually the only drug currently available for clinical management and control of urinary schistosomiasis. We systematically reviewed metrifonate and other antischistosomal compounds as a second-line drug should resistance to praziquantel develop. We searched all relevant databases and reference lists of articles and we also contacted experts in schistosomiasis research. One author extracted data, and assessed eligibility and methodological quality, which was cross-checked by a second person. Dichotomous outcomes were combined using relative risk (RR) and weighted mean difference (WMD) for continuous data, both with 95% confidence intervals (CI).

Twenty-four trials (6315 participants) met the inclusion criteria. Compared with placebo, participants receiving metrifonate had fewer parasitological failures at one to three months' follow-up and at three to 12 months. Egg reduction rate was over 90%, and no adverse events were reported. One metrifonate dose was inferior to three doses given fortnightly (both used 10 mg/kg). Praziquantel (standard single 40 mg/kg oral dose) was more effective than placebo at reducing parasitological failure up to 12 months follow-up. Egg reduction rates were improved with praziquantel (over 95% versus 5.3% to 64% with placebo). Mild to moderate adverse events were recorded in two trials. A comparison of metrifonate (10 mg/kg x 3, once every 4 months for one year) with praziquantel (standard dose) showed little difference in

parasitological failure. For praziquantel, there was no difference in effect between 20 mg/kg x 2, 30 mg/kg x 1, and 20 mg/kg x 1, and the standard dose in all outcomes. One small trial of artesunate showed no obvious benefit compared with placebo and artesunate-praziquantel combination was similar to praziquantel alone.

The systematic review showed that praziquantel and metrifonate are effective treatments for urinary schistosomiasis and have few adverse events. Metrifonate requires multiple administrations and is therefore operationally less convenient in community-based control programmes. Evidence on the artemisinin derivatives or combination therapies need further research. Based on the findings, we suggested that metrifonate should be considered for re-inclusion in the WHO Model List of Essential Medicines.

In **Chapter 4**, we highlighted implications for public health of the findings in chapter 3 and discussed methodological issues and research needs. A major observation was that most studies included in the systematic review were insufficiently powered, lacked standardization in assessing and reporting outcomes, and had other methodological limitations. The majority of trials had no proper sample size calculation and ended up being underpowered. Generation of allocation sequence was adequate in less than half of the trials and only four out of the 24 trials adequately concealed allocation and described the methods used. Also we observed that all the trials conducted in the early 1990s and before did not conceal allocation except one trial although lack of concealment of allocation overestimates effect size by more than 40%. Considerable proportions of patients were lost during follow-up, particularly in trials with repeated dosing and long follow-up periods. For instance, 17 trials registered losses of <10% for short follow-up periods (1-3 months), but losses increased considerably (in some trials approaching 50%), when follow-up lasted longer than 3 months further compromise the statistical power of already underpowered trials. Suboptimal quality resulted in few studies meeting our inclusion criteria. The criteria for diagnosis and hence sensitivity, and classification of infection intensity varied greatly between different trials. There was considerable variation in the timing of post-treatment assessments. Finally, there was confusion about how to express treatment outcomes. In this review the primary outcomes were (i) parasitological failure and (ii) egg reduction rate, but these two measures were variably reported as cure rate, failure rate, cumulative failure rate or prevalence for parasitological failure, and as a median, arithmetic mean or geometric mean for egg reduction rate. Even the calculation of geometric mean varied; some investigators considered only the positive individuals, whilst others included the negatives and introduced a correction factor of plus 1. The latter becomes problematic after treatment when most of the remaining infections are light, as it may overestimate egg count values.

We concluded that new schistosomiasis trials must be conducted to contemporary standards of clinical research paying particular attention to quality issues and adopt agreed criteria.

Chapter 5 investigates health-seeking behaviour for schistosomiasis-related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana. Such integration may be potentially sustainable and cost-effective. We conducted a questionnaire-based field study in a Ghanaian village endemic for both urinary and intestinal schistosomiasis to determine whether infected individuals self-reported to health centres or clinics and to identify factors that influenced their decision to seek health care. A total of 317 subjects were interviewed about having signs and symptoms suggestive of schistosomiasis: blood in urine, painful urination, blood in stool/bloody diarrhoea, abdominal pain, diarrhoea, swollen abdomen and fatigue within 1 month of the day of the interview. Fever (for malaria) was included as a disease of high debility for comparison.

Around 70% with blood in urine or painful urination did not seek health care, whilst diarrhoea, blood in stool, abdominal pain and fever usually led to action (mainly self-medication, with allopathic drugs being used four to five times more often than herbal treatment). On average 20% of schistosomiasis-related signs and symptoms were reported to health facilities either as the first option or second and third alternative by some of those that self-medicated. A few of those who visited a clinic or health centre as first option still self-medicated afterwards. Children under 10 years and adults were more likely to seek health care than teenagers. Also, females were more likely to visit a health facility than males of the same age groups. Socio-economic status and duration of symptoms did not appear to affect health-seeking behaviour. 'Do not have the money' (43%) and 'Not serious enough' (41%) were the commonest reasons for not visiting a clinic. We concluded that the regular health service shows some potential in passive control of schistosomiasis as 20-30% of people visited a health facility as first or second option although the proportion was somewhat small.

In **Chapter 6** we investigated health seeking behaviour from increased sample size over our earlier study (Chapter 5) to improve statistical power and to learn whether patterns of health seeking behaviour are consistent across other parts of Ghana to get better insight into regional characteristics that may influence health seeking behaviour for schistosomiasis-related symptoms.

The study confirmed earlier results which showed three main health care seeking practices namely, "Doing nothing", "Self-medicating" and "Visiting a health facility". For schistosomiasis-related symptoms or fever, many people tried self-medication (usually with allopathic drugs) and a reasonable number did not health seek health care. Overall, about 20% of all urinary and intestinal schistosomiasis-related

symptoms were reported to a health facility, which was lower than the 30% for fever. Strikingly, patients with urinary symptoms show very low tendency to seek care compared to fever and to a lesser extent, intestinal symptoms. The rate of health care seeking is lowest for symptoms with chronic characteristics, but when patients take action, they are slightly more likely to report to a health facility. In a multivariate logistic regression analysis, perceived severity consistently showed to be the most important predictor of both health care seeking in general and visiting a health facility for those that take action.

Chapter 7 evaluates quantitatively integrated schistosomiasis control from passive case finding studies in Ghana. Passive case finding based on adequate diagnosis and treatment of symptomatic individuals with praziquantel by the health care facilities is a minimum requirement for integrated schistosomiasis control. Two field studies were conducted in Ghana to obtain quantifications about the steps in this process: (1) a study of health-seeking behaviour, in chapter 5, through interview of individuals with reported schistosomiasis-related symptoms; (2) a study of the performance of the Ghanaian health system with regard to schistosomiasis case management by presenting clinical scenarios to health workers and collecting information about availability of praziquantel. It appeared that cases of blood in urine (the most typical symptom of *S. haematobium*) and blood in stool (the most typical symptom of *S. mansoni*) have a very small probability of receiving praziquantel (4.4% and 1.4%, respectively) from health facilities. Programmes aimed at making the drug available at all levels of the health care delivery system and encouraging health-seeking behaviour through health education are not likely to increase these probabilities beyond 30%. This is because many cases with blood in urine do not consider it serious enough to seek health care, and blood in stool usually requires (imperfect) diagnostic testing and referral. We therefore conclude that additional control activities, especially for high-risk groups, will remain necessary.

Chapter 8 reviews the research questions and the results of our studies in the context of literature and describes the implications for schistosomiasis control. We discussed the importance of tools to monitor praziquantel resistance, the impact of population treatment on transmission of the infection and prospects of passive case-finding for schistosomiasis-related symptoms within the regular health care delivery in Ghana. The conclusions that follow from the research of this thesis are as follows: (1) Current evidence indicates that resistance against praziquantel in Senegal is unlikely, but its possibility cannot be ruled out; (2) Both praziquantel and metrifonate are safe and efficacious in the treatment of urinary schistosomiasis; (3) Most schistosomiasis trials are insufficiently powered, lack standardization in assessing and reporting outcomes, and also have other methodological limitations; and (4) The

health services in Ghana show potential in diagnosing and treating schistosomiasis, but the number of patients visiting a health facility is low. The recommendations are: (1) Metrifonate should be reincluded in the WHO model list of essential medicines; (2) New schistosomiasis trials must keep to contemporary standards of clinical research; and (3) Passive case finding remains potentially the most effective and sustainable schistosomiasis control strategy in Ghana, but it should be supplemented with additional control options such as school health programme and community directed treatment.

Samenvatting

Dit proefschrift richt zich op het vaststellen van de behandelresultaten van geneesmiddelen tegen schistosomiasis en op de mogelijkheden om de ziektebestrijding van schistosomiasis te integreren in de reguliere gezondheidszorg van Ghana.

Hoofdstuk 1 introduceert het schistosomiasisprobleem, de beschikbare geneesmiddelen, bestrijdingsstrategieën en de onderzoeksvragen die in dit proefschrift aan de orde komen. Schistosomiasis is een tropische parasitaire worminfectie die gekenmerkt wordt door een complexe transmissie waarin een zoetwaterslak als tussengastheer dient. Er is een urinaire (door *Schistosoma haematobium* wormen) en een intestinale (*S. mansoni*) vorm, en voor beide is praziquantel het gebruikelijke geneesmiddel. Schistosomiasis kan een acute aandoening zijn, maar meestal is het chronisch. Naar schatting 780 miljoen mensen lopen er kans op, en meer dan 200 miljoen zijn geïnfecteerd. Dit leidt tot een geschatte ziektelast van 4,5 miljoen DALY's (ziektegecorrigeerde levensjaren) door schistosomiasis per jaar, waarvan 85% is geconcentreerd in Afrika beneden de Sahara. Recente studies suggereren echter dat de last nog veel groter kan zijn, omdat er in de berekeningen geen rekening is gehouden met ziektespecifieke sterfte en met lichte ziekteklachten. Schistosomiasis is gerelateerd aan armoede, maar ook watergerelateerde ontwikkelingen zoals stuwdammen vergroten de kansen op overdracht, en maken daarmee de ziektelast groter. Tot nu toe zijn er vier belangrijke bestrijdingsstrategieën toegepast met wisselende resultaten: gezondheidseducatie, schoonwatervoorziening, slakkenbestrijding en behandeling. De huidige aanpak is door de gemeenschap georganiseerde behandeling met een standaarddosis van 40 mg/kg praziquantel. Het gebruik van praziquantel is enorm toegenomen als gevolg van het streven van de Wereld Gezondheidsorganisatie (WHO) om tegen het jaar 2010 minstens 75% van de kinderen op lagere schoolleeftijd en andere risicogroepen in hoogendemische gebieden te behandelen. Dit beleid wordt onder meer uitgevoerd door het *Schistosomiasis Control Inititative* (*SCI*) via de behandeling van miljoenen schoolkinderen in een aantal landen. Hoewel er zorgen zijn om resistentie tegen praziquantel, is dat tot op heden niet aangetoond.

De zogenaamde 'verticale benadering', d.w.z. bestrijding naast de reguliere gezondheidszorg, bleek moeilijk vol te houden, zowel wat betreft de uitvoering als de kosten. Integratie in de bestaande gezondheidszorgstructuren, de 'horizontale benadering', lijkt een meer levensvatbare optie. De hoeksteen is deugdelijke klinische zorg voor patiënten die zich melden bij een gezondheidspost met schistosomiasisgerelateerde

klachten. In 2001 werd deze horizontale benadering onderschreven door een groep experts op een bijeenkomst op de WHO. Echter, er was toen nog nauwelijks kennis over hoeveel patiënten met schistosomiasisgerelateerde klachten daadwerkelijk gezondheidsposten bezoeken en welke factoren een rol spelen bij de beslissing om zorg te zoeken.

Dit proefschrift bestaat uit twee delen. Deel I richt zich op de analyse van bestaande gegevens om verdere kennis over behandeling van schistosomiasis te verkrijgen, met nadruk op praziquantel. Ook worden alternatieven voor praziquantel onderzocht. Deel II beschrijft veldstudies in Ghana naar determinanten van hulpzoekgedrag voor schistosomiasisgerelateerde symptomen, om daarmee de haalbaarheid van geïntegreerde bestrijding te bepalen. Voor Deel I zijn de volgende onderzoeksvragen geformuleerd: (1) Is er bewijs voor resistentie tegen praziquantel bij de behandeling van *S. mansoni* infectie; (2) Wat zijn de leemtes in onze kennis over de behandeling van schistosomiasis; (3) Wat zijn de mogelijkheden van andere geneesmiddelen tegen schistosomiasis dan praziquantel. En voor Deel II: (4) Wat zijn de determinanten voor hulpzoekgedrag bij schistosomiasisgerelateerde klachten in Ghana; en (5) Wat zijn de sterke en zwakke kanten van geïntegreerde ziektebestrijding van schistosomiasis in de reguliere gezondheidszorg in Ghana?

Hoofdstuk 2 richt zich op praziquantel voor de behandeling van infecties met *S. mansoni* en resistentieontwikkeling. De behandeling van *S. mansoni* infecties met de standaarddosis van 40 mg/kg praziquantel geeft meestal bij meer dan 70% van de patiënten genezing (d.w.z. geen *Schistosoma* eieren in de ontlasting). Echter, in Senegal werden ongebruikelijk lage genezingspercentages van 18% tot 38% gemeld, wat aanleiding gaf tot vermoedens over resistentie tegen praziquantel. Nieuwe studies in hetzelfde gebied gaven wederom lage genezingscijfers, terwijl de uitkomsten wel normaal waren voor oxamniquine, een alternatief geneesmiddel voor *S. mansoni*.

Wij hebben een meta-analyse uitgevoerd van onderzoeksgegevens uit verschillende locaties om factoren te identificeren die verband houden met de uitkomst van behandeling van bevolkingen met praziquantel. Op basis van een systematisch literatuuronderzoek hebben we 11 studies (uit de periode 1983 tot 1999) geschikt bevonden voor deze analyse. Het bleek dat de hoge intensiteiten van infectie voor behandeling de lage genezingscijfers in Senegal voor een deel konden verklaren. Zelfs een medicijn dat 95% van de wormen doodt zou in Senegal nog steeds veel mensen geven met genoeg overlevende wormen om de infectie te detecteren. De erg gevoelige diagnostiek die in Senegal werd gebruikt heeft verder bijgedragen aan de slechte genezingscijfers. Echter, na correctie voor deze factoren bleek Senegal

nog steeds een bescheiden maar statistisch significante lagere genezingskans te geven, zodat resistentie niet geheel kan worden uitgesloten.

Hoofdstuk 3 gaat over de behandeling van urinaire schistosomiasis. Praziquantel is feitelijk het enige geneesmiddel dat nu beschikbaar is voor behandeling en bestrijding van urinaire schistosomiasis. Wij hebben een systematisch literatuuronderzoek gedaan naar metrifonate en andere anti-schistosomiasis bestanddelen die een alternatief zouden kunnen zijn mocht er resistentie tegen praziquantel ontstaan. In totaal 24 studies (met 6315 deelnemers) voldeden aan de inclusiecriteria. Deelnemers die metrifonate ontvingen hadden in vergelijking met placebo's minstens tot een jaar na behandeling minder vaak parasieten. De reductie in eiproductie was meer dan 90% en er werden geen bijwerkingen gerapporteerd. Het gebruik van één dosis metrifonate was beduidend minder effectief dan drie doses elke twee weken (beiden bij 10 mg/kg). Een kleine studie naar artesunate liet geen duidelijk voordeel zien in vergelijking met de placebo, en de combinatie artesunate en praziquantel had een vergelijkbaar effect als alleen praziquantel.

Dit systematische literatuuronderzoek toonde aan dat praziquantel en metrifonate beide effectieve geneesmiddelen zijn voor urinaire schistosomiasis, zonder veel bijwerkingen. Bij metrifonate moeten er wel meerdere doses worden toegediend en daarom is het in de praktijk minder handig in bestrijdingsprogramma's. Om het nut van artemisinine-derivaten of combinatietherapieën te bewijzen is meer onderzoek nodig. Gebaseerd op onze bevindingen stellen wij voor om te overwegen metrifonate opnieuw op te nemen in de WHO-lijst van essentiële medicijnen.

In **Hoofdstuk 4** geven we een kritische analyse van de methodologische aspecten van de geneesmiddelenstudies in hoofdstuk 3. De meeste studies in het literatuuronderzoek hadden vooraf geen berekening over de studieomvang gedaan en waren daardoor onvoldoende groot. En veel patiënten haalden het eind van de studies niet, soms bijna 50%, vooral bij studies naar herhaalde behandeling met lange tussenpozen. Bij slechts vier van de 24 studies was de toekenning van patiënten aan de studiearmen blind uitgevoerd, waardoor het effect met minstens 40% werd overschat. Uiteindelijk was maar een gering aantal studies goed genoeg om deel uit te maken van onze overzichtsstudie. Die studies werden verder nog gekenmerkt door een grote variatie in gebruikte diagnostiek. De belangrijkste maten voor behandelresultaten waren (i) de fractie mensen die nog parasieten heeft en (ii) de gemiddelde eiproductie, maar deze twee maten werden onder verschillende benamingen gerapporteerd, en de eiproductie werd ook nog eens op verschillende manieren berekend. Met name het al dan niet meenemen van nulmetingen geeft heel verschillende uitkomsten bij het berekenen van het geometrisch gemiddelde, vooral als (door de behandeling) de intensiteit van infectie laag is. We concluderen dat

nieuwe schistosomiasisstudies naar het effect van medicijnen moeten voldoen aan hedendaagse standaarden voor klinisch onderzoek, waaronder kwaliteitsaspecten en het gebruik van standaard uitkomstmaten.

In **Hoofdstuk 5** onderzoeken we het hulpzoekgedrag van mensen met schistosomiasisgerelateerde symptomen binnen gezondheidszorgvoorzieningen in een Ghanees dorp waar zowel urinaire als intestinale schistosomiasis voorkomt. In totaal 317 proefpersonen zijn geïnterviewd over het hebben van klachten en symptomen die indicatief zijn voor schistosomiasis: bloed in de urine, pijn bij het plassen, bloed in de ontlasting/bloederige diarree, buikpijn, diarree, opgeblazen gevoel en vermoeidheid in de periode tot een maand voor het moment van interview. Ter vergelijking werd ook koorts (door malaria) meegenomen.

Ongeveer 70% van degenen met bloed in de urine en pijn bij het plassen bleek niet hulp te zoeken. Mensen met diarree, bloed in de ontlasting, buikpijn en koorts gingen meestal wel, voornamelijk om medicijnen te halen (waarbij reguliere geneesmiddelen vier tot vijf keer vaker werden gebruikt dan kruiden). Gemiddeld werd 20% van de schistosomiasisgerelateerde klachten gemeld bij een gezondheidspost. Sommigen die eerst een gezondheidspost of kliniek hadden bezocht gingen daarna elders medicijnen kopen. Kinderen onder de 10 jaar en volwassenen zochten vaker hulp dan tieners, en vrouwen vaker dan mannen. Sociaal-economische status en duur van de klachten bleek geen effect te hebben op het hulpzoekgedrag. “Ik heb het geld niet” (43%) en “Het is niet belangrijk genoeg” (41%) werden het vaakst gemeld als reden voor het niet bezoeken van een kliniek. We concluderen dat de reguliere gezondheidszorg nuttig kan zijn voor de bestrijding van schistosomiasis aangezien 20% tot 30% van de mensen met klachten zich meldt bij een gezondheidspost. Maar deze fractie is tamelijk laag.

Hoofdstuk 6 beschrijft net als Hoofdstuk 5 het hulpzoekgedrag, maar nu in een veel grotere groep respondenten in verschillende delen van Ghana, zodat betere statistische analyses konden worden gedaan en we konden testen of de bevindingen algemeen geldend waren. De uitkomsten van hoofdstuk 5 werden bevestigd, zoals de belangrijke rol van zelfmedicatie (meestal met reguliere geneesmiddelen) en het grote aantal mensen met schistosomiasisgerelateerde symptomen dat geen bezoek brengt aan een gezondheidspost. De mensen met chronische symptomen gaan het minst vaak op zoek naar zorg, maar verkiezen wel vaker een gezondheidspost. Bij alle onderzochte symptomen en voor verschillende Ghanese regio’s was de ervaren ernst van de ziekte de belangrijkste voorspeller van het zoeken van hulp en van de keuze voor een gezondheidspost.

In **Hoofdstuk 7** berekenen we de gevolgen van integratie van de bestrijding van schistosomiasis in de gezondheidszorg van Ghana. Adequate diagnose en behandeling met praziquantel van symptomatische individuen zijn daarbij de kerndoelstellingen. Twee veldstudies in Ghana werden uitgevoerd om meer inzicht te krijgen in de stappen van dit proces: (1) de studie beschreven in hoofdstukken 5 en 6 naar hulpzoekgedrag door schistosomiasispatiënten, en (2) een studie naar de kwaliteit van het Ghanese gezondheidszorgsysteem bij de behandeling van zulke patiënten. Dat laatste is gedaan door gezondheidswerkers te interviewen over wat ze zouden doen bij bepaalde klinische scenario's en over de beschikbaarheid van praziquantel. Het bleek dat patiënten met bloed in urine (het meest voorkomende symptoom van urinaire schistosomiasis) en bloed in de ontlasting (idem voor intestinale schistosomiasis) maar een paar procent kans hadden om praziquantel te krijgen. Initiatieven gericht op een betere beschikbaarheid van het medicijn en het verhogen van de neiging hulp te zoeken via gezondheidseducatie zullen deze kans hooguit kunnen verhogen tot zo'n 30%. Dit komt omdat te veel mensen met bloed in urine dit symptoom niet ernstig genoeg vinden, en omdat bloed in de ontlasting te weinig specifiek is en diagnostiek en verwijzing behoeft. We concluderen daarom dat aanvullende verticaal georganiseerde bestrijdingsactiviteiten nodig blijven, vooral voor risicogroepen.

Hoofdstuk 8 geeft een overzicht van de beantwoording van de onderzoeksvragen en van de belangrijkste bevindingen, vergelijkt deze met ander onderzoek, en bespreekt de betekenis voor de schistosomiasisbestrijding. De conclusies zijn als volgt: (1) De huidige gegevens laten zien dat resistentie tegen praziquantel in Senegal niet waarschijnlijk is, maar de mogelijkheid kan niet geheel worden uitgesloten; (2) Zowel praziquantel als metrifonate zijn veilig en effectief in de behandeling van urinaire schistosomiasis; (3) De meeste studies naar de werking van schistosomiasismedicijnen zijn te beperkt van omvang, missen standaardisatie in de vaststelling en rapportage van de bevindingen, en hebben ook andere methodologische beperkingen; en (4) De gezondheidsstructuren in Ghana zijn beloftevol wat betreft de diagnose en behandeling van schistosomiasis, maar het aantal patiënten dat een gezondheidspost bezoekt is nog te laag. De aanbevelingen zijn: (1) Metrifonate zou opnieuw deel uit moeten maken van de WHO-lijst met essentiële geneesmiddelen; (2) Nieuwe studies naar het effect van schistosomiasisbehandeling moeten voldoen aan de hedendaagse standaarden van klinisch onderzoek; en (3) Het behandelen van mensen die zich melden met klachten blijft op de lange termijn de meest effectieve schistosomiasisbestrijdingstrategie in Ghana, maar aanvullende maatregelen zoals behandeling via scholen en de gemeenschap zijn voorlopig ook nog nodig.

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Curriculum Vitae

Anthony Danso-Appiah was born on 4th June 1970 in Accra, Ghana. After completing SDA Secondary School at Bekwai and Nandom Boys High School, he enrolled in the University of Ghana and graduated with two majors (BSc combined honours in Nursing and Nutrition) in 1993. He enrolled in the University of Ghana Medical School in 1994 and left for the Netherlands in 1996 following the award of NUFFIC Fellowship. He studied Health Services Research and received MSc in 1997 from The Netherlands Institute for Health Sciences, Erasmus University Rotterdam. He worked temporarily with Unilever Nutrition Centre (Netherlands) in 1998 evaluating the usefulness of factors of blood coagulation system as bio-markers for predicting clinical thrombotic events. He followed a part-time course and obtained certificate in Marketing Management from the Erasmus University Rotterdam in 1997. Then, in 1998 he began a study in Epidemiology and obtained Doctor of Science (DSc) in 2001 from Erasmus University Rotterdam. With sponsorship from University of Oslo in 1998, he followed the course 'Issues in International Health Systems Development' and obtained Grade A with honours from the University of Oslo, Norway. He has also followed a number of short certificate and specialised courses. In 1999 he received Grant- funds from WOTRO/NWO for a PhD study in the Department of Public Health, Erasmus University Rotterdam to investigate Treatment Effects of Antischistosomal Drugs and Integrated Morbidity Control of Schistosomiasis within the Regular Health Service in Ghana. From January 2006 to February 2007 he worked as West Africa Co-ordinator with the International Health Group, Liverpool School of Tropical Medicine, translating evidence-based research into policy and practice. In Liverpool, he specialized in research synthesis and systematic review. In 2007 he worked as Research Fellow- Methodologist (Clinical Evidence) at the National Collaborating Centre for Women's and Children's Health, Royal College of Obstetricians and Gynaecologists, London developing clinical guidelines for the NHS in England and Wales. He was methodologist for the guideline 'Management of Diabetes and its Complications from Pre-conception to the Postnatal Period'. Since November 2007, at the invitation of the WHO, he is working on WHO commissioned systematic review with international collaborators to assess safety tolerance of drugs for the treatment and prevention of schistosomiasis- *Schistosoma heamatobium*, *S. mansoni*, *S. japonicum, S. intercalatum* and *S. mekongi*. He is also working for the International Health Group, Liverpool School of Tropical Medicine doing a systematic review on drugs for treating *S. mansoni* infections for the Cochrane Collaboration.

ERASMUS UNIVERSITEIT ROTTERDAM

Name PhD student: Anthony Danso-Appiah **Erasmus MC Department:** Public Health **Research School:** NIHES	**PhD period:** 1999 – 2009 **Promotor:** Prof. Dr. J.D.F. Habbema **Supervisor:** Dr. Sake J. De Vlas		
PhD training	**Location**	**Year**	**Workload (Hours)**
General courses			
Introduction to Health Services Research	EUR*	1996	90
Study Design	EUR	1996	60
Classical Methods for Data-analysis	EUR	1996	84
Public Health Research Methods Part I & II	EUR	1996	90
Advanced Health Services Research	EUR	1996	162
Specific courses			
Advanced Study Design Part I	EUR	1998	30
Advanced Study Design Part II	EUR	1999	30
Modern Statistical Methods	EUR	1999	48
Operational Research Applied to Health Services	EUR	1997	18
Health Status Measurements	EUR	1997	18
Planning and Evaluation of Screening	EUR	1997	30
Quant. Methods Evaluation Tropical Disease Control	EUR	1997	54
Introductory Medical Research Writing	EUR	1997	24
Cancer Epidemiology	Cambridge, UK	1997	18

Presentations at international conferences			
Integration of schistosomiasis control within the regular health services in Ghana (oral). International Symposium on High Tech & Poor Health	Amsterdam	2003	12
The horizontal approach to morbidity control of schistosomiasis in Ghana (poster). The Netherlands Foundation for Advancement of Tropical Research (WOTRO) Researchers' Day	Utrecht	2001	12
No schistosome resistance to praziquantel (poster). International colloquium on "Moving targets: parasites, resistance and access to drugs	Antwerp	2000	12
Quantitative effects of population selective chemotherapy with praziquantel on Schistosoma mansoni infection: a meta-analysis (oral). International Symposium on Schistosomiasis	Rio de Janeiro	1999	12
Are the repeated low cure rates of Praziquantel in population treatment of S. mansoni infection in Senegal due to resistance? (oral). 20th African Health Sciences Congress in Ghana	Accra	1999	12
TOTAL			786

* EUR means Erasmus University Rotterdam