Schistosomiasis Morbidity and Management of Cases in Africa

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Schistosomiasis Morbidity and Management of Cases in Africa

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Aan mijn ouders

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1

General introduction

Schistosomiasis is one of the most prevalent parasitic diseases and an important public health problem in many developing countries. The number of individuals with morbidity due to schistosome infection, and therefore the magnitude of the problem, has never been studied in detail. This information would facilitate advocacy and better planning of national and local control programmes. In the first part of this thesis, we estimated the number of individuals suffering from morbidity due to schistosome infection using data from published field studies that reported infection and morbidity, subsequently we determined the burden of disease due to schistosomiasis.

Integration of schistosomiasis control in existing health structures is a key element of sustainable control (Engels *et al.*, 2002). This implies that at least individuals affected by schistosomiasis morbidity that report at a health care facility should receive adequate diagnosis and treatment (WHO, 2002). In second part of this thesis, we assessed whether prerequisites for case management were available and if integrated schistosomiasis control was functional in health care facilities in Ghana, Mali and Senegal by interviewing health workers in the three countries.

1.1 The parasite life cycle

Schistosomiasis is caused by infection with flatworms belonging to the genus *Schistosoma* (Trematoda, Platyhelminthes). The five species that infect humans are *S. haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*. Most African countries and some countries in the Middle East are endemic for *S. haematobium* and *S. mansoni*. *S. intercalatum* has been reported in ten countries in Africa (Chitsulo *et al.*, 2000). Outside Africa, *S. mansoni* is also present in South America, esp. in Brazil. *S. mekongi* and *S. japonicum* are confined to the Far East. The five species differ in size and shape of their eggs, egg production (*S. haematobium* and *S. mansoni* 20 - 300 and *S. japonicum* 3500 eggs per worm pair per day (Jordan *et al.*, 1993)) and location within the human host and consequently cause different signs and symptoms.

Humans become infected after contact with surface water in which the intermediate host snails live (Figure 1.1). These snails shed cercariae, free living, infective schistosome larva. The release of cercariae is most pronounced around noon and starts 3 to 5 hours after the snails are exposed to light (Wolmarans *et al.*, 2002). Cercariae are positively phototropic and will therefore congregate towards the water surface where possibilities for contact with humans or animals are maximal (McKerrow and Salter, 2002). Upon contact with human skin, they adhere and apply their oral sucker (Jordan *et al.*, 1993). They respond to chemical signals, particularly medium chain fatty acids, as a signal for skin invasion. By means of both enzymes and vigorous movement the skin is penetrated. Thereafter, they shed their tail and are transformed to schistosomula, the next larval stage. These are migrate through the venules, right heart chamber and lungs via the mesenteric arteries and portal vein to the liver. In the liver the schistosomulum starts to grow until it is mature. The mature male and female worm mate in the liver and migrate to the blood vessels of the intestines (intestinal schistosomiasis caused by *S. mansoni*, *S. japonicum*, *S. mekongi* and *S.*

intercalatum) or urinary tract (urinary schistosomiasis caused by *S. haematobium*) where the females live in the gynaecophoric canal of the male worms. Here, they start laying eggs after approximately 30 days. The lifespan of adult worms ranges from 3 to 38 years (Arnon, 1990, Harris *et al.*, 1984) and thus a large number of eggs will be produced in a lifetime. Eggs migrate through the wall of the intestines or bladder and are excreted by defecation or urinating, respectively. When the excreted eggs come in contact with fresh water they hatch a miracidium, which is able to infect the intermediate snail host. In the snail, new cercariae develop by asexual reproduction.

Control measures that interrupt the life-cycle of schistosomes can be divided into (1) snail control (molluscicides), (2) prevention of water contact by humans (safe water supply and building of bridges), (3) killing of worms in the human host (chemotherapy treatment with antischistosomal drugs) and (4) prevention of surface water contamination with urine or stool (sanitation) (WHO, 1993). Health education of populations at risk for infection and development of disease can aim at reducing contact of humans with infected water bodies, increasing health care seeking behaviour for schistosomiasis-related symptoms and preventing contamination of surface water with human excreta.

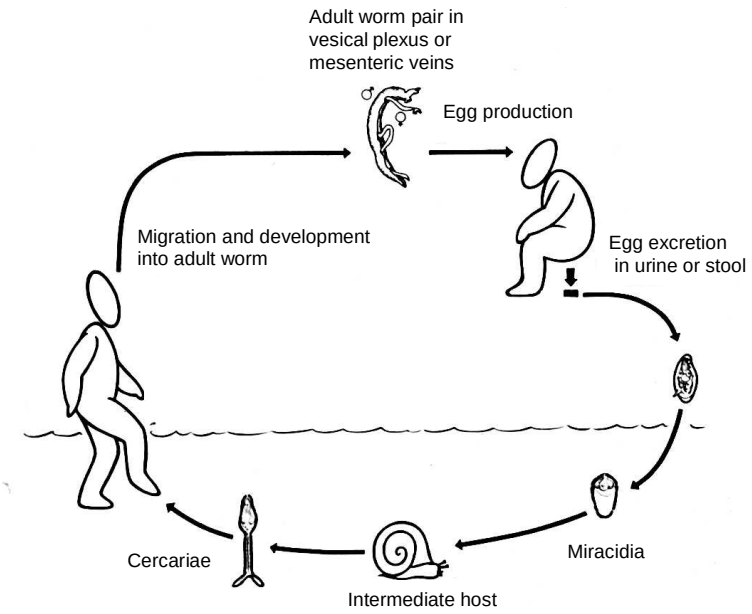

Figure 1.1: Transmission cycle of schistosomes. With kind permission of Dr. A.M. Polderman.

The studies presented in this thesis are confined to species of schistosomes that are prevalent in Africa (*S. haematobium* and *S. mansoni*). *S. intercalatum* is not discussed.

1.2 Pathogenesis

The first reaction that can occur in the definitive host is due to penetration of the skin by cercariae. Up to 40% of the schistosomula released from the cercariae will die in the skin and these can induce hypersensitivity reactions of both the immediate and delayed type (Webbe, 1981). In the stage of maturation, migration and early oviposition of the worms a form of serum sickness may develop due to the formation of immune complexes (Katayama syndrome).

Approximately 4 weeks after infection, the adult worms reach the blood vessels of the vesical plexus or the mesenteric and portal veins (Cheever *et al.*, 1977). *S. mansoni* worms are located almost entirely in the mesenteric veins. The female worms deposit eggs in the blood venules of the host, for *S. haematobium* around 160 eggs per worm pair per day and for *S. mansoni* 300 (Loker, 1983). These eggs actively penetrate the tissue of the bladder or intestines to reach the lumen of the bladder or bowels. However, 50% or more become trapped in the tissue and die within 20 days (Warren, 1978). In *S. mansoni* infection, the eggs are also transported to the liver by the blood flow where they get trapped in the sinusoids and eventually die (Pearce and MacDonald, 2002). Soluble egg antigens which are actively excreted through the egg shell induce a $CD4^+$ T-cell response which is responsible for the development of granulomas, composed of collagen fibres and cells (including macrophages, eosinophils and $CD4^+$ T-cells) (Warren, 1975, Dunne and Pearce, 1999, Stadecker, 1999). As the eggs die, the granulomas resolve and may leave fibrotic plaques.

1.3 Pathology and morbidity

1.3.1 Stage of invasion

Shortly after penetration of the skin by cercariae (within a few hours) a pruritic papular rash can occur at the site of penetration. Time between exposure and appearance of the skin lesions can also be much longer, e.g. months to years (Wood *et al.*, 1976, Eulderink *et al.*, 1994, Farrell *et al.*, 1996, Davis-Reed and Theis, 2000). The skin manifestations mainly occur in migrants and tourists coming into contact with schistosomes for the first time. However, it can also be diagnosed in sensitised persons who are re-infected by a non-human schistosome species (Health Council of the Netherlands, 2001).

1.3.2 Acute schistosomiasis

Two to 10 weeks after the initial infection the Katayama syndrome can develop, mainly in non-immune visitors to endemic areas, and more severe after *S. mansoni* infection (Hiatt *et al.*, 1979, Zuidema, 1981, Visser *et al.*, 1995). The presenting symptoms vary from general malaise to severe illness. The most common clinical findings are fever, anorexia, headache, abdominal pain, myalgia, arthralgia, diarrhoea, loss of weight, hepatomegaly, splenomegaly, and urticaria (Stuiver, 1984, Doherty *et al.*, 1996, Kager and Schipper, 2001). Less commonly there are pulmonary manifestations, shortness of breath and a dry cough

(Schwartz *et al.*, 2000). Normally, the severity of acute schistosomiasis varies with the intensity of infection as measured by egg counts (Hiatt *et al.*, 1979).

1.3.3 Early manifestations of infection

S. haematobium

Pathology in *S. haematobium* infected individuals most frequently occurs in the bladder. Lesions can be detected by cystoscopy (hyperaemia, sandy patches, polypoid lesions, vesical ulcers, granulomas and calcifications, (Abdel-Salam and Ehsan, 1978, Chen and Mott, 1989)). Nowadays ultrasonography is the main method for detecting pathology in the urinary system as it is a noninvasive and innocuous technique (Hatz *et al.*, 1992). Ultrasonography visualises intravesical masses and pseudopolyps, thickening and irregularities of the bladder wall and calcifications (Richter *et al.*, 1996). In highly endemic areas, bladder lesions can be detected in up to 89% of the population (Campagne *et al.*, 2001) and major bladder lesions in 44% (Hatz *et al.*, 1998). This pathology often regresses after treatment (Hatz *et al.*, 1990). Bladder lesions produce the early symptoms (terminal) haematuria, dysuria, urinary frequency and supra pubic pain. It has been suggested that the loss of blood causes anaemia (Gerritsen *et al.*, 1953, Farid *et al.*, 1968), but no conclusive evidence has been provided from population-based studies: Some found a positive relationship between *S. haematobium* infection and anaemia (Greenham, 1978, Bretagne *et al.*, 1985, Cooppan *et al.*, 1986), whereas others did not find any association (Ejezie and Ade-Serrano, 1981, Wilkins *et al.*, 1985, Prual *et al.*, 1992, Befidi-Mengue *et al.*, 1993).

Female genital schistosomiasis is a common manifestation of *S. haematobium* infection (prevalence rate ranging from 30 to 75% in *S. haematobium* infected women) and occurs when *S. haematobium* eggs are deposited in the female genital tract (Poggensee and Feldmeier, 2001). The main clinical characteristics are irregular menstruation, pelvic pain, vaginal discharge and post-coital bleeding, other possible consequences may be infertility, miscarriage or ectopic pregnancy (Poggensee *et al.*, 1999). It has been suggested that female genital schistosomiasis may enhance risk of contracting HIV (Feldmeier *et al.*, 1994).

S. mansoni

Individuals infected with *S. mansoni* can have pathologic changes in the intestines, liver and sometimes the spleen. The main lesions detected in the intestines are colonic polyposis, focal fibrosis and inflammation (Chen and Mott, 1988). These lesions may present with (bloody) diarrhoea, blood in the stool, abdominal pain or more general symptoms of infection such as weakness or fatigue (Gryseels, 1992). Several studies showed a positive relationship between frequency and severity of symptoms and intensity of infection (Arap Siongok *et al.*, 1976, Sukwa *et al.*, 1986), but others did not report this (Smith *et al.*, 1979, Gryseels and Nkulikyinka, 1989). Pathological changes in the liver include periportal fibrosis, also called Symmers' fibrosis (clay pipestem fibrosis), which is often reversible

after adequate treatment (Doehring-Schwerdtfeger *et al.*, 1992, Boisier *et al.*, 1998). If not treated, it may result in portal hypertension due to physical obstruction of the portal blood flow (see *S. mansoni*: late pathology and morbidity). Ultrasonography can detect periportal fibrosis and is also useful in assessment of liver and spleen enlargement.

1.3.4 Late manifestations of infection

S. haematobium

Eggs deposited in the tissues of the ureters can cause obstructive uropathy, i.e. hydroureter and hydronephrosis, which can be visualised by ultrasonography. One study showed that presence of lesions was related to the intensity of infection both on individual and population level (Traoré *et al.*, 1998b). Obstructive uropathy can give rise to gradual compression of the kidney parenchyma eventually causing non-functioning kidney. The glomerular and proximal tubular function of the kidneys may remain intact for a long time (Browning *et al.*, 1984, Cooppan *et al.*, 1987).

The evidence supporting a causal relationship between infection with *S. haematobium* and squamous cell bladder carcinoma is considerable (Mostafa *et al.*, 1999). Chronic irritation and inflammation caused by *S. haematobium* infection in the bladder could initiate premalignant lesions or act as a promoting agent for conversion of pre-malignant lesions to the malignant state. The induction of bladder cancer in laboratory animals by infection with schistosomes supports this theory (Schwartz, 1981).

S. mansoni

Severe clinical manifestations of *S. mansoni* infection such as ascitis, haematemesis, oedema and peri-umbilical varices, are seen in a relatively small proportion of patients with persistent or heavy infections (Gryseels and Nkulikyinka, 1990, Gryseels, 1992, Boisier *et al.*, 1995). These symptoms develop due to the pre-sinusoidal obstruction of the blood flow and resulting portal hypertension. Some populations seem to be more vulnerable to the development of severe symptoms than others (Gryseels, 1989). This can partly be explained by varying intensities of infection but differences in genetic make-up of the parasite or the human host may also be responsible. The evidence is controversial for a role of *S. mansoni* infection in the development of hepatocellular carcinoma (Chen and Mott, 1988).

1.3.5 Ectopic morbidity

Schistosome eggs are also detected outside the genitourinary (*S. haematobium*) or gastro-intestinal (*S. mansoni*) system. Frequently reported ectopic locations are the skin and, more importantly, the central nervous system. Egg-induced lesions in the brain are reported to cause epilepsy (Raper, 1948), and lesions in the spinal cord may present with acute transverse myelitis (Norfray *et al.*, 1978, Suchet *et al.*, 1987). Definite diagnosis is difficult

and therefore incidence or prevalence figures of ectopic schistosomiasis in the central nervous system not available.

1.3.6 Subtle morbidity

Intuitively, schistosome infections will have an indirect effect on nutrition, growth and physical fitness due to resulting diarrhoea, decreased appetite or loss of nutrients. In recent years, evidence for a relationship between schistosome infection and subtle morbidity is increasing (Stephenson, 1993) but not always supportive (Corbett *et al.*, 1992, Ekanem *et al.*, 1994). Studies reporting a relationship between schistosome infection and impaired cognitive development are rare and inconclusive (Nokes and Bundy, 1994).

1.4 Mortality

The main cause of mortality due to *S. haematobium* infection is non-functioning kidney, from obstructive uropathy (Forsyth *et al.*, 1970, Lehman *et al.*, 1970). Patients with bilateral non-functioning kidney develop uraemia, which presents with disturbances in almost all organ systems. Without a successful renal transplantation the patient will die from the imbalances in one or more of these systems (e.g. metabolic acidosis, hyper or hypokalemia). Also, squamous cell bladder carcinoma may contribute to death attributed to *S. haematobium* infection. Mortality due to *S. mansoni* infection can result form haematemesis, cor pulmonale and liver failure (Kloetzel, 1967). The overall schistosomiasis mortality rate in Brazil was 0.30/100,000/year in 1993 (Katz, 1998). A study in Sudan, in a population with 53% prevalence of infection reported a crude mortality rate of schistosomiasis of 51/100,000/year (Kheir *et al.*, 1999). In a highly infected population in Uganda (89% prevalence of infection) it was 2,600/100,000 of which at least 25% was due to *S. mansoni* infection, resulting in 650/100,000/year (Ongom and Bradley, 1972).

1.5 Public health impact in Africa

1.5.1 Distribution

The most recent estimates show that 37 sub-Saharan African countries are endemic for *S. haematobium* with an estimated average prevalence of infection of 26%. Thirty-eight are endemic for *S. mansoni* with average prevalence of infection of 18% (Brooker *et al.*, 2000b, Chitsulo *et al.*, 2000) (Figure 1.2). Of North African countries 7 are endemic for *S. haematobium* and 4 for *S. mansoni*.

In general, the 5 to 15 year age-group shows the highest prevalence and intensity of infection (Gryseels and Polderman, 1987, Stelma *et al.*, 1993, Traoré *et al.*, 1998a, Guyatt *et al.*, 1999b). Therefore, this group also suffers most from disease caused by the infection (Gryseels and Nkulikyinka, 1990, Vester *et al.*, 1997). It is still not clear to what extent the high prevalences and intensities of infection in this age group are due to differences in water contact, gradual development of immunity or other age-related factors, e.g. hormones (Butterworth, 1994, Gryseels, 1994). Severe disease usually follows after many

years of infection and is therefore mainly found in the older age groups (Boisier *et al.*, 1995, Kardorff *et al.*, 1997).

Gender is generally not considered an important determinant for schistosome infection. If a difference is reported between the sexes then boys are more often infected than girls (Boisier *et al.*, 1995, Guyatt *et al.*, 1999a). The few studies that reported on specific occupations as risk factor for infection observed a higher prevalence in occupational groups with more intensive water contact (e.g. fishermen compared to farmers) (Abdel-Wahab *et al.*, 1980, El-Hawey *et al.*, 1995).

1.5.2 The existing estimates of the burden of schistosomiasis

Current estimates of the global number of individuals with morbidity due to infection with schistosomes were based on the assumption (not derived from data) that 10% of 200 million individuals infected with schistosomiasis have severe clinical disease (i.e. 20 million) and that of the remaining 180 million 50-60% also have symptoms (WHO, 1993). More detailed evidence based global morbidity figures are not available. The WHO Global Burden of Disease Initiative used a simplistic method to estimate the burden of schistosomiasis (see *10.1.5*) (Murray and Lopez, 1996). A low disability weight (0.005 compared to 0.172 for a malaria episode) was attributed to all schistosome infections. For sub-Saharan Africa, it was estimated that 1.3 million DALYs (Disability Adjusted Life Years, sum of years of life lost and years of life lived with disability) are lost due to schistosome infection compared to e.g. 27 million for malaria. A flaw in this calculation is that not all infected individuals will experience morbidity. On the other hand, not all individuals with schistosomiasis-related disease are found positive at standard screening (De Vlas *et al.*, 1992, Utzinger *et al.*, 2001). Moreover, in the Global Burden of Disease calculations, mortality due to schistosome infection is based on figures only including death directly attributable to schistosomiasis. Most mortality caused by schistosomiasis will be due to aspecific symptoms developed many years after the initial infection, making it difficult to ascribe them to the infection. Experts in schistosomiasis morbidity believe that the calculations of the Global Burden of Disease Initiative significantly underestimate the burden of schistosomiasis and need revision (WHO, 2002).

1.6 Schistosomiasis control by chemotherapy

1.6.1.Treatment

Praziquantel is the drug of choice for treatment of schistosomiasis caused by any of the human schistosome species (WHO, 2002). It is a safe single dose drug, which can be prescribed to all age groups at a dose of 40 mg kg^{-1} body weight. The drug has become significantly less costly, average treatment is now available for less than 0.30 US$, opening perspectives for a more generalised access to the drug (Engels *et al.*, 2002). Alternatives

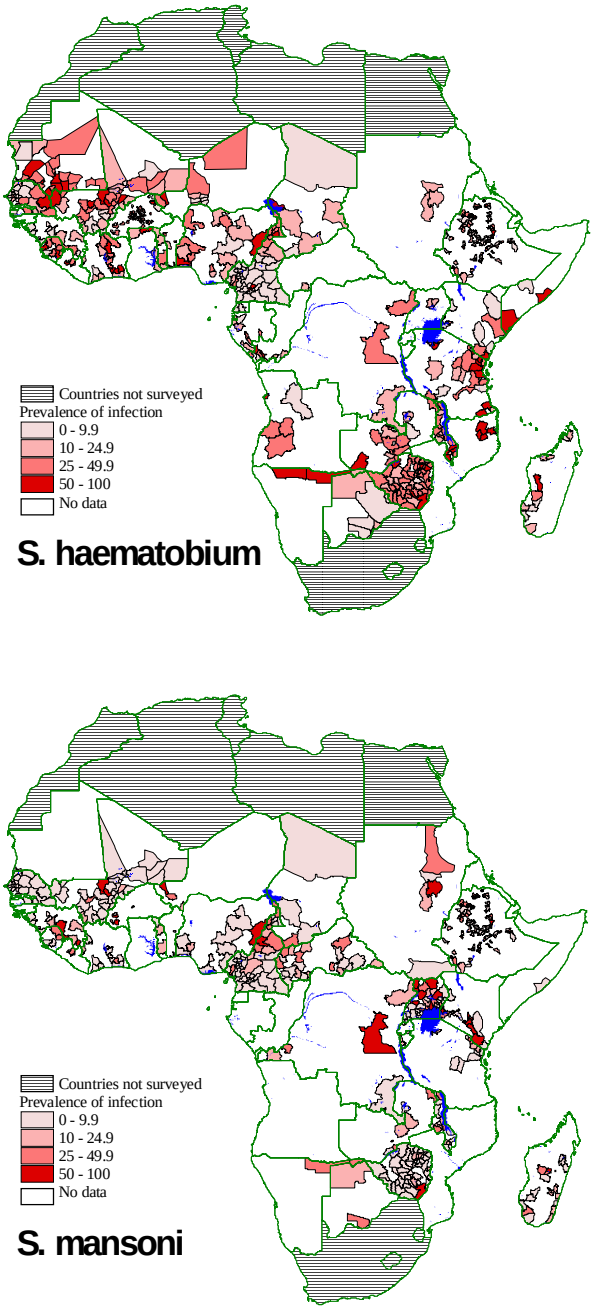

Figure 1.2: Prevalence of *S. haematobium* and *S. mansoni* infection by district. With kind permission of Dr. S. Brooker.

such as oxamniquine or metrifonate are more expensive and active against only one species, *S. mansoni* and *S. haematobium* respectively.

Population based chemotherapy with praziquantel is highly effective in reducing prevalence and especially intensity of infection, however, re-infection rates are high (Dabo *et al.*, 2000, N'Goran *et al.*, 2001) due to continuous exposure to infected water bodies (Gryseels and Polderman, 1991). Therefore, morbidity control (and not infection control) is the strategy endorsed by the WHO Expert Committee (WHO, 1985). Symptoms of both intestinal and urinary schistosomiasis regress promptly after treatment (Hatz *et al.*, 1998, Doehring-Schwerdtfeger *et al.*, 1992, Boisier *et al.*, 1998). Repeated treatment during childhood is suggested to reduce or delay the risk of development of severe urinary and hepatic morbidity (WHO, 2002).

Widespread use of praziquantel has raised concern about the development of resistance (Brown, 1994, Cioli, 1998), especially after the observation of very low cure rates in a highly endemic area in Northern Senegal (Gryseels *et al.*, 1994, Stelma *et al.*, 1995). This initiated studies to examine possible resistance against praziquantel (Renganathan and Cioli, 1998, Gryseels *et al.*, 2001, Danso-Appiah and De Vlas, 2002). Both field and laboratory studies concluded that there is so far no convincing evidence for praziquantel-resistance. The low cure rates in Northern Senegal were attributed to high initial worm loads and intense transmission in the area. However, the suspicion that praziquantel resistant/tolerant schistosomes might emerge requires preparedness to deal adequately with such a situation (Cioli, 1998).

1.6.2 Morbidity control by integration of activities in regular health services

In 1984, the World Health Organization (WHO) introduced a strategy that aimed at schistosomiasis morbidity control (WHO, 1985). Initially, they advocated a vertical approach, i.e. community wide treatment campaigns co-ordinated and organised at the national level. The long-term results were often disappointing, and these programmes were expensive and not sustainable after withdrawal of external donor funding (Gryseels, 1989). The 1991 WHO Expert Committee on the Control of Schistosomiasis 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, emphasised that the first essential component should be adequate clinical care for patients presenting at the health care facilities (passive case detection) (Engels *et al.*, 2002). This is also the only option for patients in countries without a (national) schistosomiasis control programme. Recommendation for achieving adequate schistosomiasis case management were (WHO, 1993):

1. Symptomatic cases should be treated with praziquantel at all levels of the health care system

2a. Diagnostic tests (e.g. urine filtration or centrifugation for *S. haematobium* and Kato Katz faecal smear for *S. mansoni*) should be used for diagnosis in the health care facilities with diagnostic facilities.

2b. Case detection should be performed on presenting symptoms (symptom-based treatment) in the health care facilities without diagnostic facilities

Applying these recommendations requires sufficient knowledge by the health workers of the presenting symptoms of schistosomiasis and of the recommended treatment. Furthermore, diagnostic materials and praziquantel should be available. There are no systematic studies assessing the availability of these prerequisites in health systems in schistosome endemic countries. Evaluation of schistosomiasis case management is necessary to determine whether this first essential component of integrated schistosomiasis control is functional in countries that adopted this strategy and what the situation is concerning schistosomaisis control in countries without a schistosomiasis control programme.

1.6.3 Steps in passive case detection

Even when the recommendations mentioned above for integration of schistosomiasis control in the Primary Health Care System are met, morbidity control by passive case detection does not have to be a success. This can be evaluated in more detail by studying all steps in the series *infection – pathology – disease – health care visiting – treatment (within the health system) – reduction of infection* (Figure 1.3).

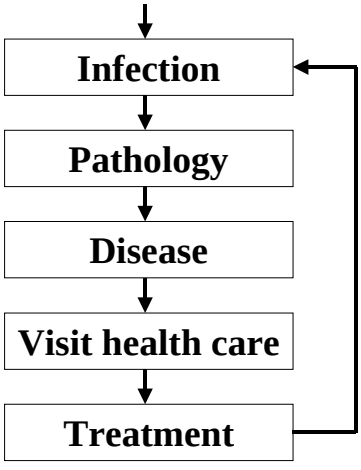

Figure 1.3: Steps in passive case detection. With kind permission of Dr. S.J. de Vlas.

Briefly, infection gives rise to the development of early morbidity that is supposed to act as a warning sign. This early morbidity is the motivation for individuals to seek health care so that subsequent treatment can prevent development of chronic disease. Some knowledge, attitudes and practices studies show that individuals in endemic areas seem to be aware of the symptoms of schistosomiasis when having them (Taylor *et al.*, 1987, Aryeetey *et al.*, 1999, Useh and Ejezie, 1999) and consider them serious (Amazigo *et al.*, 1997, Taylor *et al.*, 1987). Schistosomiasis was also reported to be part of life and not to necessitate a visit to a health care facility (Asenso-Okyere *et al.*, 1998). In a recent study in Southern Ghana, only a minority (20-30%) of the villagers with haematuria or blood in stool in the past month reported that they had visited a health care facility, whereas many more (40-50%) reported that they had practised self-medication (Danso-Appiah *et al.*, 2001). Reported reasons for not visiting regular health care facilities were mainly 'not have the money for seeking health care' or 'considering the symptom not serious enough'. Even if the next step, treatment of patients with schistosomiasis symptoms, is functional, morbidity control will only be achieved if individuals with symptoms report at the health care facility. Finally, praziquantel should cure patients from the disease. It has been shown that both symptoms caused by *S. haematobium* and *S. mansoni* infection are reversible when treated with praziquantel (Sukwa *et al.*, 1987, Polderman and de Caluwe, 1989, Campagne *et al.*, 2001).

1.6.4 Organisation of the health care system

In most African countries, health care can be obtained from the traditional and the orthodox ('modern') health system. Traditional healers can be divided into two main categories, spiritual healers (priest/priestess, witch doctors, Moslem koranic teachers, diviners) and herbalists (Yeboah, 2000). The essential practice of all traditional healers is the constant utilisation of magico-religous acts and concepts (Twumasi and Bonsi, 1975). Most traditional healers are specialised in treating one to several diseases, mainly chronic, non-life threatening diseases of high incidence (Imperato, 1970). Effective traditional treatments for schistosomiasis are unknown. Visiting the traditional health sector with symptoms caused by schistosomiasis will only delay curative treatment for schistosomiasis.

Most health services in Africa are organised according to the primary health care principle (WHO, 1978). In these health systems, the emphasis is on community participation, decentralisation of services, harmony between health service characteristics and country resources, importance of cultural aspects, search for equity and integration of disease specific vertical programmes. In primary health care, the first level is defined as the initial health establishment (normally health centre or health post) that forms the first point of encounter between the population and the health system. Health care facilities at this level are normally staffed with medical assistants or nurses, helped by other personnel such as ward assistants. Their main task is providing basic primary care (curative and preventive) to all individuals in the community for which they are responsible. This includes patients presenting with symptoms of early schistosomiasis infection, such as haematuria and blood in stool. Cases that can not be handled at the initial level, because they cannot be treated as

outpatients or require techniques not available at the primary level (including patients with long-term consequences of schistosomiasis, such as kidney failure and haematemesis), are referred to the secondary level, often the district hospital. These are normally managed by a medical doctor who is in charge of all activities occurring within the hospital. The role of the referral level is to ensure the continuity of curative care. Finally, there could be a tertiary and fourth level at regional and national level: hyper-specialised hospitals that have sophisticated equipment and function as research and teaching units. Most countries also have private clinics run by nurses, medical assistants or doctors and mission clinics or hospitals that may play an important role in the total supply of health care.

In Africa, self-medication is widespread among all classes of people (Abosede, 1984, Asenso-Okyere *et al.*, 1998). It is often the first action taken for symptoms such as diarrhoea and fever (Danso-Appiah *et al.*, 2001). Drugs are available in private or governmental pharmacies, on the market or from drug peddlers (persons who travel from place to place to sell drugs). Accessibility of praziquantel if often low, both due to the high price and the unavailability at health care facility level (personal communication B. Gryseels).

1.6.5 Measuring quality of case management

Passive detection of schistosomiasis cases requires adequate health worker performance and availability of pre-requisites for case management in health care facilities. These components have never been studied for schistosomiasis case management. However, valuable methods have been developed for studying case management of other diseases. The most straightforward method is direct observation of health care provider - patient contacts. For example, a study in Kenya evaluating quality of sexually transmitted disease (STD) case management found that 14 to 48% of the observed health care providers correctly applied the WHO recommendations for STD care (Voeten *et al.*, 2001). Observations of contacts between health workers and children with diarrhoea revealed that history taking was adequate in 20-50% of the encounters and Oral Rehydration Therapy advised by more than 50% of the health workers in Pakistan (Nizami *et al.*, 1996) and by 83% in a study in Mozambique (Cutts *et al.*, 1988). Malaria cases were correctly diagnosed by about 50% of the health workers in south-eastern Tanzania, 30% of the confirmed malaria cases did not receive antimalarial treatment (Font *et al.*, 2001). Observation studies give detailed information about health care provider - patient contacts (Beracochea *et al.*, 1995), but high costs and the fact that it is time-consuming are disadvantages of this method. It is also prone to bias due to changes in behaviour of health workers in the presence of observers (Béria *et al.*, 1998, Beullens *et al.*, 1997). Another frequently applied method for studying case management is the examination of medical charts. This does not give detailed information about the case management process and is often hampered by poorly recorded critical information (e.g. only the diagnosis is written down and not the presenting symptoms) (Beullens *et al.*, 1997). In a

study of the clinical management of malaria, about half of the patients received treatment without a diagnosis being recorded on the patient chart (Ofori-Adjei and Arhinful, 1996).

The use of simulated or standardised patients does not have these drawbacks. Detailed complete information can be collected without influencing the health care provider - patient contact (Beullens *et al.*, 1997). Studies using both simulated patients and a written questionnaire showed that the results obtained by the questionnaire included more superfluous actions which had been considered unnecessary according to an existing consensus standard (Rethans and van Boven, 1987). Disadvantages of using simulated patients are that it requires extensive training of volunteers in simulating diseases (Woodward *et al.*, 1985). Furthermore, not all health workers are eager to participate in these kind of studies because they sometimes consider them intrusive (Rethans and van Boven, 1987a). A method used by one study was the presentation of clinical scenarios for assessing typical case management (Ofori-Adjei and Arhinful, 1996). The obtained results were comparable to those of the medical chart audit.

It is clear that all methods for measuring quality of health care have advantages and disadvantages. The most adequate method depends on the research question, desired outcome and the available time and means. In our study in Ghana, the use of the simulated patients was rejected because the medical doctors would consider it offensive and merely a test of their competence. As the observation method would only allow us to study a limited number of health care facilities due to personnel and time constraints and posed other disadvantages, we chose to present clinical scenarios to the health workers in different types of health care facilities.

1.7 Aims of the thesis

Current estimates of the Global Burden of schistosomiasis lack detail and precision. Experts in schistosomiasis morbidity believe that the total burden of schistosomiasis has significantly been underestimated by the Global Burden of Disease Initiative. Our **first aim** is to determine more accurate estimates of disease and death due to schistosomiasis.

Morbidity control is the main goal of most initiatives to control schistosomiasis. According to WHO recommendations this should be integrated in the Primary Health Care system with at least adequate diagnosis and treatment of patients reporting with symptoms of schistosomiasis at the health system. Our **second aim** is to explore the quality of schistosomiasis case management and to determine the probability that patients with symptoms from *S. haematobium* or *S. mansoni* infection that report at the health system receive adequate treatment.

1.8 Outline of the thesis

This thesis consists of two parts, Part I deals with the first and Part II with the second aim.

In Part I, we present a method to associate population prevalences of schistosome infection and resulting morbidity (**Chapter 2)**. Results were provided for *S. mansoni*.

Associations between *S. haematobium* infection and morbidity were estimated in **Chapter 3**. In both chapters, we also studied the effect of determinants such as study setting (children vs. communities) and geographical area (North, West and East Africa) on the associations. The effect of recall period length on the association of *S. haematobium* infection with prevalence of self-reported haematuria determined by questionnaires was assessed in **Chapter 4**. Finally, in **Chapter 5**, we estimated the number of individuals with morbidity due to schistosome infection based on the associations determined in **Chapters 2 and 3**, country prevalences of infection derived from Geographic Information Systems (GIS) and other sources, and taking into account heterogeneity of community prevalences within countries.

In Part II of the thesis, we present the results of interviews of health workers employed at different levels of the health systems in Ghana, Mali and Senegal (**Chapters 6, 7 and 8**). In particular, we assessed whether the main prerequisites for diagnosis and treatment of schistosomiasis patients were available in the health care facilities: knowledge of the presenting symptoms and recommended treatment and availability of diagnostic materials and drugs. The findings were related to the objectives of (national) schistosomiasis control programmes or to the WHO recommendations for passive case detection. In **Chapter 9**, we studied schistosomiasis case management by presenting four clinical scenarios, two presenting with symptoms compatible with *S. haematobium* and two with symptoms compatible with *S. mansoni* infection, to health workers in Ghana and Mali.

In **Chapter 10**, we discussed our choices, e.g. the used equation and the degree of heterogeneity and the consequences of these choices for the estimated morbidity. We also attempted to re-calculate the burden of schistosomiasis and compared our estimates with those of the Global Burden of Disease Initiative. In this chapter we also compared, the quality of schistosomiasis case management in the three countries and discussed differences between the countries and the advantages and disadvantages of passive case detection.

Part I

Estimating the burden of schistosomiasis morbidity in Africa

2

Associating community prevalence of *Schistosoma mansoni* infection with prevalence of signs and symptoms

Van der Werf, M. J., De Vlas, S. J., Looman, C. W. N., Nagelkerke, N. J. D., Habbema, J. D. F. and Engels, D. (2002). Associating community prevalence of *Schistosoma mansoni* infection with prevalence of signs and symptoms. *Acta Tropica*, **82,** 127-137

Abstract

Information on the prevalence of morbidity is needed for re-calculation of the Global Burden of Disease (WHO) due to *Schistosoma mansoni*. This study presents a statistical association which can be used to predict the prevalence of morbidity from the prevalence of *S. mansoni* in a community. We collected data from field studies reporting prevalence of infection and prevalence of morbidity. Data on infection prevalence were standardised to a default diagnostic sensitivity (i.e. Kato-Katz technique 41.7 mg). The data were described by an expression related to logistic regression.

We determined associations between prevalence of infection and prevalence of early morbidity (diarrhoea, blood in stool and abdominal pain), hepatosplenic morbidity and late morbidity (haematemesis and ascitis). Diarrhoea and blood in stool due to *S. mansoni* infection mainly occurs in communities with a high prevalence of infection. An influence on hepatosplenic morbidity is already present at low community prevalence of infection. For the aspecific symptom abdominal pain we did not find an association.

Introduction

An estimated 229 million individuals are infected with schistosomes in Africa (Brooker *et al.*, 2000b). Schistosomiasis was ranked 78 in the list of causes of Disability Adjusted Life Years (DALYs) for the world (Murray and Lopez, 1996)(DALY is a time-based health-outcome measure that includes weights for time spent in less-than-perfect health, it is the sum of years of life lost and years of life lived with disability (Murray and Lopez, 1997a)). This ranking was based on prevalence data of schistosome infection, which was assigned a disability weight. In order to better determine the years lived with disability, we consider it more appropriate to estimate the number of individuals with signs and symptoms caused by infection with schistosomes and to allocate a disability weight to each specific sign or symptom.

Infection with *Schistosoma mansoni* results in non-specific signs and symptoms, which can also be caused by several other diseases. Therefore, it is interesting to determine the prevalence of morbidity due to *S. mansoni*. We have aggregated data of *S. mansoni* morbidity and identified associations between prevalence of infection and prevalence of morbidity taking into account a baseline level of morbidity attributable to other causes. The results were used to estimate the number of morbidity cases caused by *S. mansoni* infection in a community.

Methods

Identification of signs and symptoms of Schistosoma mansoni *infection and data collection*

The definition of morbidity used in the Global Burden of Disease Initiative is 'condition which causes loss of welfare'. We identified signs and symptoms caused by infection with *S. mansoni* from the literature (Chen and Mott, 1988, Jordan *et al.*, 1993). The information was used to prepare a list of major signs and symptoms. This was presented to experts in schistosomiasis morbidity and revised following discussions.

We searched Pubmed (United States: National Library of Medicine) to identify all published articles reporting field studies in unselected study populations on *S. mansoni* infection and morbidity. The references of the collected articles were checked for additional articles.

Quantitative information about prevalences of *S. mansoni* infection and morbidity was stored in a common database. Only data collected before treatment were included.

Relating morbidity to infection

In our analysis we related prevalence of morbidity (y-axis) to prevalence of infection (x-axis) on population level. The morbidity in low prevalence communities then gives information on a possible base-line morbidity due to other causes.

An expression related to the logistic regression curve, meeting the following requirements was used:

1. the possibility of a baseline morbidity due to other causes, defined by parameter a ($a \geq 0.0$)
2. a horizontal start of the curve at $x = 0$ and $y = a$, so first derivative = 0.0 in $(0,a)$
3. the curve should rise monotonously and be able to finally (but not necessarily) reach a prevalence of morbidity of 1.0
4. the curve should show a biologically realistic association between prevalence of infection and prevalence of morbidity, so no steep increase before $x = 0.5$ and thereafter a levelling off. A realistic point of inflection (where the curve is steepest, so second derivative equals 0.0) should usually be on the right-hand side of prevalence $x = 0.5$. This condition forces a horizontal start of the curve, precluding substantial morbidity at low prevalence of infection

Any equation $y = a + (1 - a)\exp(f_x)/(1 + \exp(f_x)) = (a + \exp(f_x))/(1 + \exp(f_x))$ covers the area between a (base-line morbidity) and 1. In logistic regression f_x is the linear predictor, e.g. $f_x = B + Cx$. Due to requirement 2, we have used $f_x = B + C \log x$ ($C > 1$). The resulting equation $y = (a + \exp(B)\, x^C) / (1 + \exp(B)\, x^C)$ has a derivative of $y' = 0$ when $x \rightarrow 0$.

By replacing $\exp(B)$ with b ($b > 0$) and C with c ($c > 1$) one obtains the following relationship between prevalence of infection x and prevalence of morbidity y:

$$y = (a + bx^c)/(1 + bx^c) \qquad (1)$$

We used Systat (version 3.0, 1986) to estimate the values of parameters a, b and c by fitting the equation to all n data points, assuming a binomial distribution and assigning each data point i ($i = 1, \ldots, n$) equal weight. The latter assumption was motivated by the fact that morbidity (y) is determined by many more factors (e.g. the community base-line morbidity) than sheer population size. Thus, we maximised the log-likelihood

$$\sum_i y_i \log(\hat{y}_i) + (1 - y_i) \log(1 - \hat{y}_i) \qquad (2)$$

where y_i is the observed prevalence of pathology/morbidity and $\hat{y}_i$ is the predicted prevalence of pathology/morbidity from Equation 1, given prevalence of infection x.

When condition 4 was not met, we chose an alternative two parameter curve (which is a special case of standard equation $y = (a + bx^c)/(1 + bx^c)$) with point of inflection at 1.0

$$x_{infl} = ((c-1)/(b(c+1))^{1/c} = 1.0 \quad (3)$$

hence

$$b = (c-1)/(c+1) \quad (4)$$

resulting in

$$y = \frac{a + \frac{c-1}{c+1}x^c}{1 + \frac{c-1}{c+1}x^c} \quad (5)$$

We present a, b and c for the best fitting standard curve, if applicable (see point 4 above). If the point of inflection is chosen at 1.0, b is presented as $b_{1.0}$.

Prevalence data from each reported community or school were included as independent data points. Therefore, each study could contribute multiple data points. We first determined whether there was evidence for a different association between prevalence of infection and morbidity for children and adults. If the data did not suggest a different association then data for children and adults were aggregated to community prevalence data.

From the fitted expression, the curve with $a = 0$ (no baseline)

$$y = bx^c/(1 + bx^c), \quad (6)$$

or its alternative with $b = b_{1.0} = (c-1)/(c+1)$ was subsequently used to make predictions for any community on the morbidity potentially due to *S. mansoni* infection.

Standardisation of prevalence of infection

In field studies, the prevalence of *S. mansoni* infection is commonly determined from stool samples. The quantity of stool examined differs between studies. Studies examining large quantities of stool (more sensitive technique) find more individuals positive for *S. mansoni*. Less sensitive techniques leave (many) individuals with (light) infection undetected. We standardised the reported prevalences according to the expected outcome of a default diagnostic technique (i.e. a single 41.7 mg Kato-Katz faecal sample) to be able to compare prevalences obtained by the examination of different quantities of stool.

Calculation of standardised prevalences has been done by using an existing model for *S. mansoni* egg count variation (De Vlas *et al.*, 1992). This model assumes repeated individual egg counts to reflect an underlying distribution of worm (pair) burdens. The number of worms is assumed to follow a negative binomial distribution NegBin (M, k) with mean worm load M and aggregation parameter k. The distribution of worm pairs x is the result of applying

a mating process to the distribution of worms, assuming a ratio of male to female worms of 1:1.

The faecal egg counts for a given number of worms follow a negative binomial distribution NegBin (f_x,r) with mean egg counts being proportional $f_x = hx$ to the number of worm pairs number x, and an aggregation parameter r. Parameter h relates worm pair burdens to the expected number of eggs and therefore depends on the total amount of stool examined (h = 0.001 times the amount of stool in mg). So for the default, h = 0.042 (42 mg of stool).

The value of r is determined by two components of aggregation: r_1 depends on the number of specimens and the duration between successive measurements and has been estimated at 1.27 times the number of specimens for about month-to-month variation in *S. mansoni*; r_2 depends on the total amount of stool examined and has been estimated at 0.0896 times the amount of stool in mg, so that e.g. r_2 = 3.74 for 41.7 mg stool samples. The overall aggregation parameter r can be described conveniently using the expression $1/r = 1/r_1 + 1/r_2$ (De Vlas, 1996). A user-friendly modelling device was developed to fit the model and to predict the prevalence for the default if another sensitivity had been applied in the included study. In case no information was available on the amount of stool examined, we assumed the default of a single 41.7 mg Kato-Katz stool sample.

Values of r_1, r_2 and h are assumed to be universally applicable. M (mean worm load) and k (aggregation parameter) have to be estimated for each population or age group concerned. Thus, at least two indicators of the level of infection in a population must be available. There are three combinations which meet this condition: (1) prevalence and (geometric) mean egg count, (2) number of individuals in at least three intensity groups, (3) number of individuals in at least two intensity groups and (geometric) mean egg count in all groups together. The model has been fitted to all studies meeting the above criteria. If only one indicator was provided (i.e. the prevalence of infection), the median value of k was imputed from other studies (k = 0.4).

Figure 2.1 illustrates the effect of standardisation of prevalence of infection for the data from blood in stool and *S. mansoni*. It is clearly shown how the values from studies based on non-default amounts of stool shift to the left (initially more stool used) or the right (less stool used). Each prevalence of infection that was standardised resulted in estimations of a combination of parameters M and k.

Results

Table 2.1 lists possible consequences of infection with *S. mansoni*, identified by literature research and expert consultation. For most signs and symptoms no or few data from field studies were available. Therefore, we had to restrict the analysis to the association of prevalence of *S. mansoni* and prevalence of early morbidity (diarrhoea, bloody diarrhoea, blood in stool and abdominal pain), advanced hepatosplenic morbidity (hepatomegaly and splenomegaly) and late morbidity (haematemesis and ascitis).

Data for diarrhoea, bloody diarrhoea, blood in stool, abdominal pain and haematemesis were obtained from studies that collected data by questionnaire method. In these studies participants were asked for symptoms during a specified period. This recall period differed widely between studies: It could be as short as one day (the last 24 hours) or as long as 1 year. More than a quarter of the studies did not even specify the period. If prevalences were reported for more than one recall period, we used the results from the recall period closest to 2 weeks.

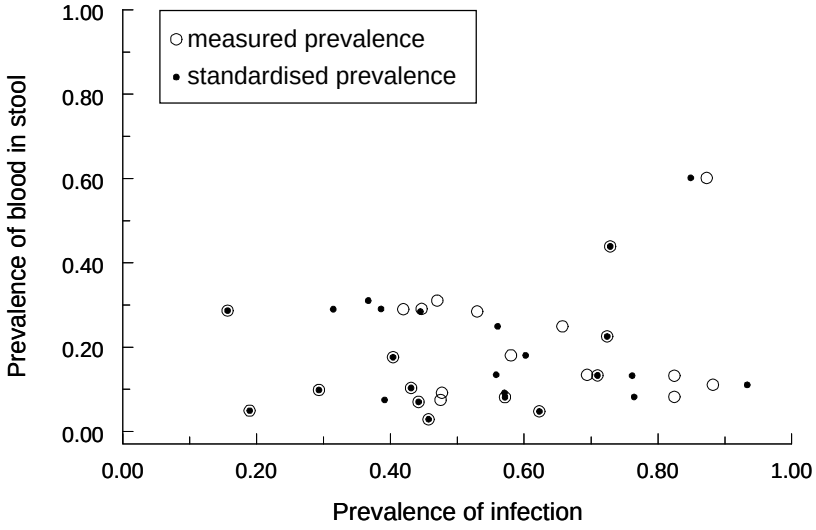

Figure 2.1: Blood in stool as a function of measured and standardised prevalences of *S. mansoni* infection. Both points overlap if the default amount of stool (single 41.7 mg) was used. Shifted points are located on the same vertical line. Data from 2 school surveys are not included because they did not have to be standardised (Lengeler *et al.*, 2000, Utzinger *et al.*, 2000).

The difference between the symptoms diarrhoea, bloody diarrhoea and blood in stool is gradual and difficult to distinguish. Most studies reporting prevalence of bloody diarrhoea did not report prevalence of blood in stool and vice versa. For analysis, we focussed on diarrhoea and blood in stool. Diarrhoea and blood in stool are easily distinguishable, whereas diarrhoea and bloody diarrhoea and blood in stool and bloody diarrhoea tend to overlap. We also chose for 'blood in stool' because it is considered to be highly specific for intestinal schistosomiasis (Gryseels, 1992).

Data for splenomegaly, hepatomegaly and ascitis were obtained from studies that collected data by clinical examination. The studies measured hepatomegaly at mid-sternal level (MSL) or mid-clavicular level (MCL). The cut-off points for defining hepatomegaly differed between the studies (MSL: from palpable to > 5cm, MCL: from palpable to > 4 cm). Some studies reported prevalence of hepatomegaly for more than one cut-off point. The results of the lowest reported cut-off point (i.e. palpable) were used for our analysis.

The cut-off points for defining splenomegaly also differed between the studies (Hackett grade 1 and 2 and comparable measures). When studies reported prevalence of splenomegaly for more than one cut-off point, the lowest cut-off point (i.e. palpable spleen) was used.

Table 2.1: Consequences of infection with *S. mansoni*.

Stage	Pathology	Morbidity
Invasion		Cercarial dermatitis
Acute	Due to foreign antigens and metabolites excreted when egg production starts	Katayama fever: fever, chills, weakness, weight loss, headache, anorexia, nausea, vomiting, diarrhoea, dry cough, hepatosplenomegaly, bloody diarrhoea, urticaria, peri-orbital oedema, bronchospasm
Early	Colonic polyposis, focal fibrosis and granulomatous inflammation	(Bloody) diarrhoea Blood in stool Abdominal pain
Early and late		Anemia
Late	Portal hypertension	Hepatosplenomegaly Ascites Oedema Oesophageal varices Haematemesis Liver failure Cor pulmonale
	Ectopic lesions (CNS)	Convulsions, paralysis
Subtle		Reduction of growth Impaired cognitive development Reduced physical fitness
Mortality	Portal hypertension	Liver failure Cor pulmonale Haematemesis

We did not find a significant effect of age or recall period on any of the studied associations. Therefore, curves were fitted for the aggregated data. For comparison, we show separate data points for children and adults in Figures 2.2 and 2.3 if available. Therefore, the number of data points in the figures does not equal the number of data points used for the analysis.

Figure 2.2 shows the association of prevalence of infection and prevalence of early intestinal morbidity. Fifteen studies reported data on prevalence of infection and diarrhoea for 25 communities, 21 studies reported blood in stool for 136 communities and 22 studies reported data on abdominal pain for 25 communities. For measuring the prevalence of diarrhoea, studies used recall periods ranging from 1 day to 8 weeks, but often not specified. According to the figure only at high prevalences, *S. mansoni* infection contributes to diarrhoea.

Figure 2.2: Association between prevalence of *S. mansoni* infection and prevalence of early morbidity (next page). The association with diarrhoea is described by Equation (1) and a = 0.222, b = 0.272 and c = 7.702, for blood in stool, a = 0.186, b = 0.689 and c = 4.948 and the estimation of the association with abdominal pain was inconclusive. Studies reporting diarrhoea (Abdel-Wahab *et al.*, 1990, Arap Siongok *et al.*, 1976, Boisier *et al.*, 1995, De Clercq *et al.*, 1985, Gremillion *et al.*, 1978, Gryseels and Polderman, 1987, Gryseels, 1991, Guimaraes *et al.*, 1985, Hiatt, 1976, Hiatt and Gebre-Medhin, 1977, Mungomba and Kalumba, 1995, Ndamba *et al.*, 1991, Smith *et al.*, 1979, Sukwa *et al.*, 1986, Tshikuka *et al.*, 1996), studies reporting blood in stool (Abdel-Wahab *et al.*, 1990, Abdel-Wahab *et al.*, 2000a, Arap Siongok *et al.*, 1976, Barakat *et al.*, 2000, Boisier *et al.*, 1998, De Lima e Costa *et al.*, 1985, El-Hawey *et al.*, 2000, Eltoum *et al.*, 1993, Gremillion *et al.*, 1978, Guimaraes *et al.*, 1985, Habib *et al.*, 2000, Hiatt, 1976, Hiatt and Gebre-Medhin, 1977, Homeida *et al.*, 1996, Lengeler *et al.*, 2000, Mungomba and Kalumba, 1995, Nooman *et al.*, 2000, Ongom and Bradley, 1972, Ripert *et al.*, 1982, Sukwa *et al.*, 1986, Utzinger *et al.*, 2000) and studies reporting abdominal pain (Abdel-Wahab *et al.*, 2000a, Arap Siongok *et al.*, 1976, Barakat *et al.*, 2000, De Lima e Costa *et al.*, 1985, El-Hawey *et al.*, 1995, El-Hawey *et al.*, 2000, Gremillion *et al.*, 1978, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Gryseels, 1991, Guimaraes *et al.*, 1985, Habib *et al.*, 2000, Hiatt, 1976, Hiatt and Gebre-Medhin, 1977, Kabatereine, 2000, Mungomba and Kalumba, 1995, Ndamba *et al.*, 1991, Nooman *et al.*, 2000, Ripert *et al.*, 1982, Smith *et al.*, 1979, Stelma *et al.*, 1994).

Figure 2.3: Association between prevalence of *S. mansoni* infection and prevalence of hepatosplenic morbidity (next page). The association for hepatomegaly (MSL) is described by the Equation (5) with a = 0.183, $b_{1.0}$ = 0.217 and c = 1.555, for hepatomegaly (MCL), a = 0.143, $b_{1.0}$ = 0.165 and c = 1.395 and for splenomegaly, a = 0.094, $b_{1.0}$ = 0.120 and c = 1.272. Studies reporting hepatomegaly (MSL) (Abdel-Wahab *et al.*, 1990, Abdel-Wahab *et al.*, 2000b, Arap Siongok *et al.*, 1976, Barreto *et al.*, 1985, Bulsara *et al.*, 1985, De Clercq *et al.*, 1985, De Lima e Costa *et al.*, 1985, El-Hawey *et al.*, 1995, Eltoum *et al.*, 1993, Forsyth and Bradley, 1966, Fulford *et al.*, 1991, Gabr *et al.*, 2000, Gaye *et al.*, 1991, Gremillion *et al.*, 1978, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Gryseels, 1991, Guimaraes *et al.*, 1985, Hammam *et al.*, 2000b, Hammam *et al.*, 2000a, Hiatt and Gebre-Medhin, 1977, Homeida *et al.*, 1996, Johansen *et al.*, 1994, Kardorff *et al.*, 1997, Omer *et al.*, 1976, Ongom and Bradley, 1972, Ripert *et al.*, 1982, Sukwa *et al.*, 1986, Wiselka *et al.*, 1988), studies reporting hepatomegaly (MCL) (Abdel-Wahab *et al.*, 1990, Abdel-Wahab *et al.*, 2000a, Arap Siongok *et al.*, 1976, Barakat *et al.*, 2000, Bulsara *et al.*, 1985, Corbett *et al.*, 1992, El-Hawey *et al.*, 2000, Friis and Byskov, 1987, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Guimaraes *et al.*, 1985, Habib *et al.*, 2000, Hiatt, 1976, Hiatt and Gebre-Medhin, 1977, Kardorff *et al.*, 1997, Lehman *et al.*, 1976, Nooman *et al.*, 2000, Smith *et al.*, 1979, Stelma *et al.*, 1994, Sukwa *et al.*, 1986, Wiselka *et al.*, 1988) and studies reporting splenomegaly (Abdel-Wahab *et al.*, 1990, Abdel-Wahab *et al.*, 2000a, Arap Siongok *et al.*, 1976, Barakat *et al.*, 2000, Barreto *et al.*, 1985, Boisier *et al.*, 1995, Bulsara *et al.*, 1985, Corbett *et al.*, 1992, De Clercq *et al.*, 1985, De Lima e Costa *et al.*, 1985, El-Hawey *et al.*, 1995, El-Hawey *et al.*, 2000, Eltoum *et al.*, 1993, Forsyth and Bradley, 1966, Friis and Byskov, 1987, Fulford *et al.*, 1991, Gabr *et al.*, 2000, Gaye *et al.*, 1991, Gerspacher-Lara *et al.*, 1998, Gremillion *et al.*, 1978, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Gryseels, 1991, Guimaraes *et al.*, 1985, Habib *et al.*, 2000, Hammam *et al.*, 2000b, Hammam *et al.*, 2000a, Hiatt, 1976, Homeida *et al.*, 1996, Johansen *et al.*, 1994, Kardorff *et al.*, 1997, Kloetzel and Schuster, 1987, Lehman *et al.*, 1976, Martins *et al.*, 1998, Nooman *et al.*, 2000, Omer *et al.*, 1976, Ongom and Bradley, 1972, Ripert *et al.*, 1982, Smith *et al.*, 1979, Sukwa *et al.*, 1986, Tshikuka *et al.*, 1996, Wiselka *et al.*, 1988).

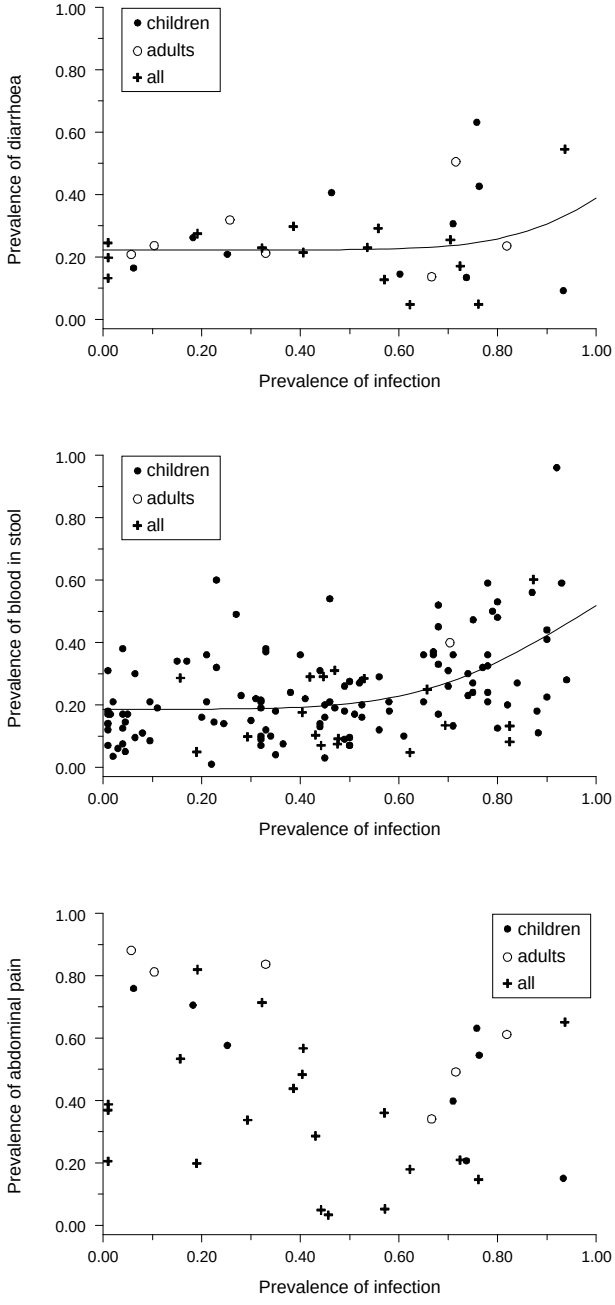
children
adults
all
Prevalence of diarrhoea
Prevalence of blood in stool
Prevalence of abdominal pain
Prevalence of infection
0.00
0.20
0.40
0.60
0.80
1.00

Figure 2.2

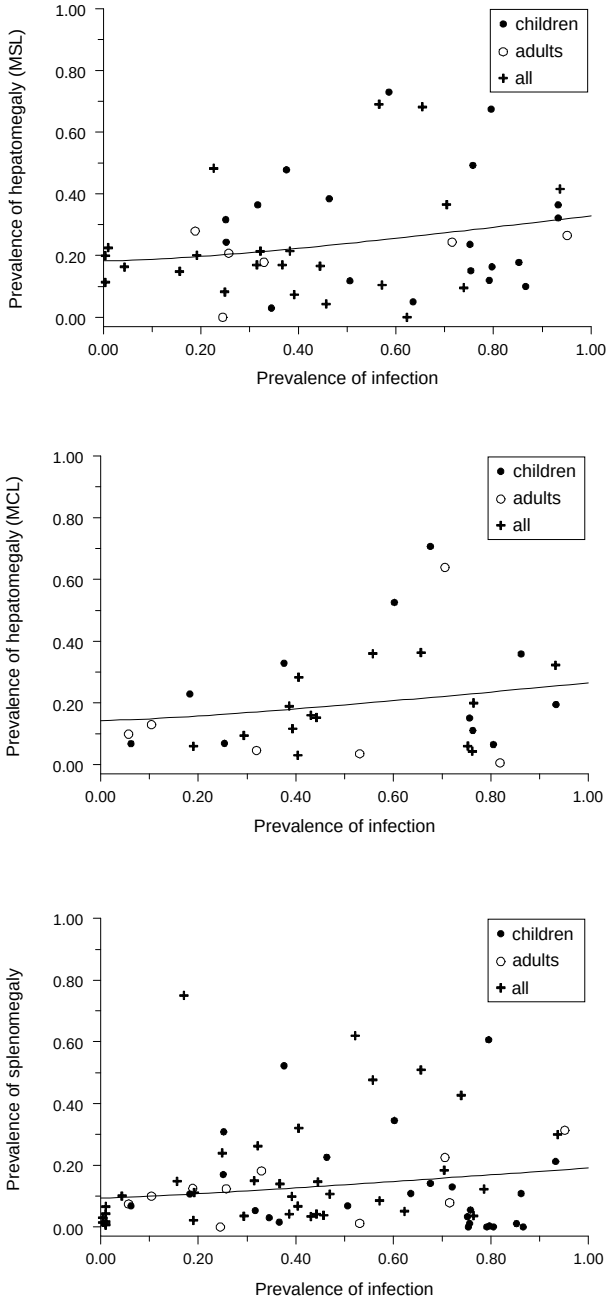
Prevalence of hepatomegaly (MSL)
Prevalence of infection
children
adults
all
Prevalence of hepatomegaly (MCL)
Prevalence of infection
children
adults
all
Prevalence of splenomegaly
Prevalence of infection
children
adults
all
0.00
0.20
0.40
0.60
0.80
1.00

Figure 2.3

For measuring the prevalence of blood in stool the collected studies used recall periods ranging between 1 day to 1 year and often the recall period was not specified. Two studies provided most data points, (Utzinger *et al.*, 2000) 60 data points and (Lengeler *et al.*, 2000) 54 data points. The shape of the individually fitted curves for the data points from Utzinger et al. (2000) and Lengeler et al. (2000) was comparable to the shape of the curve for the other data points. Therefore, a combined curve for all data points was fitted.

The recall period used for measuring abdominal pain differed widely between the field studies (from 1 day to 8 weeks, often not specified). Estimating the association between prevalence of *S. mansoni* infection and prevalence of abdominal pain was non-conclusive.

The association between infection and prevalence of hepatosplenic morbidity is presented in Figure 2.3. Thirty studies reported data on prevalence of infection and hepatomegaly (MSL) for 41 communities, 22 studies reported data on prevalence of infection and hepatomegaly (MCL) for 25 communities and 44 studies reported splenomegaly for 61 communities. The fitted standard Equation (1) for hepatomegaly (MSL), hepatomegaly (MCL) and splenomegaly had a point of inflection < 0.5. Therefore, we used Equation (5) with point of inflection at 1.0.

Figure 2.4 shows the association between prevalence of infection and prevalence of late morbidity. Twelve studies reported data on prevalence of infection and haematemesis for 17 communities and six studies reported ascitis for eight communities. The fitted standard Equation (1) for haematemesis and ascitis had a point of inflection < 0.5. Therefore, we used Equation (5) with point of inflection at 1.0.

Table 2.2 shows the predicted prevalences of morbidity for different prevalences of infection (prevalence persons positive if a 41.7 mg stool sample is examined by Kato Katz method) from the associations.

Table 2.2: Prevalence estimates for diarrhoea, blood in stool, hepatomegaly (MSL), hepatomegaly (MCL), splenomegaly, 'haematemesis ever' and ascitis due to *S. mansoni* infection.

Morbidity \ Infection	0.15	0.50	0.85
Diarrhoea	0.000	0.001	0.072
Blood in stool	0.00	0.02	0.24
Hepatomegaly (MSL)	0.01	0.07	0.14
Hepatomegaly (MCL)	0.01	0.06	0.12
Splenomegaly	0.011	0.047	0.089
Haematemesis ever	0.002	0.006	0.011
Ascitis	0.0004	0.0012	0.0021

The estimated prevalences are calculated from the curves described in Figs 2-4.

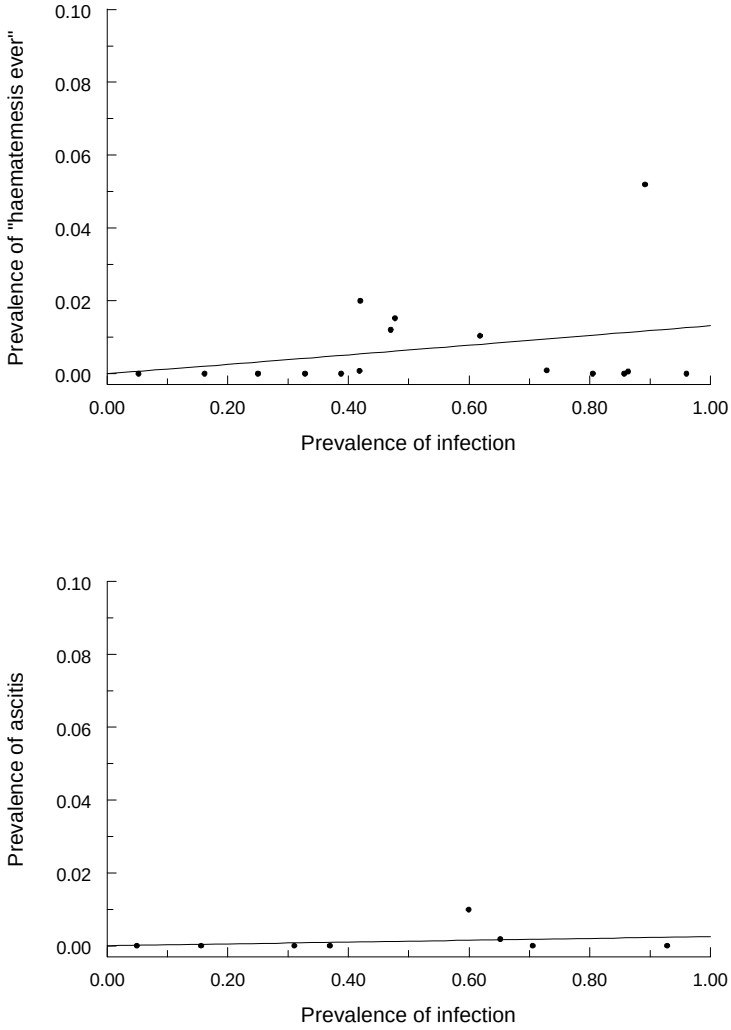

Figure 2.4: Association between prevalence of *S. mansoni* infection and prevalence of late morbidity. The association with reported haematemesis 'ever' is described by the alternative Equation (1) combined with Equation (4), $a \approx 0$, $b_{1.0} = 0.0133$ and $c = 1.027$ and for ascitis, $a \approx 0$, $b_{1.0} = 0.00249$ and $c = 1.005$. Studies reporting haematemesis (Boisier *et al.*, 1995, De Lima e Costa *et al.*, 1985, Friis and Byskov, 1987, Gaye *et al.*, 1991, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Hiatt, 1976, Homeida *et al.*, 1996, Kabatereine, 2000, Kardorff *et al.*, 1997, Ongom and Bradley, 1972) and studies reporting ascitis (Boisier *et al.*, 1998, De Lima e Costa *et al.*, 1985, Gryseels and Polderman, 1987, Gryseels, 1988, Gryseels and Nkulikyinka, 1990, Strickland *et al.*, 1982).

Discussion

This is the first time that all available information from field studies on *S. mansoni* has been used to estimate associations between prevalence of *S. mansoni* infection and prevalences of morbidity. For early symptoms of infection with *S. mansoni* and late signs and symptoms caused by portal hypertension we present an association between prevalence of infection and prevalences of signs and symptoms in a community. Data available for morbidity caused by invasion of cercariae, symptoms of acute infection and subtle morbidity (Table 2.1) were insufficient to use the developed methodology.

Some points should be taken into account for interpretation of the associations. First, we did not find an association between prevalence of infection and prevalence of abdominal pain in this 'meta-analysis'. This is supported by the fact that of the 22 studies that were used for the analysis, only 7 reported significantly more abdominal pain in groups with a higher intensity of infection, whereas 12 did not find this association (three studies did not report prevalence of abdominal pain by intensity of infection group). Thus, also within studies the relation between infection and prevalence of abdominal pain is not obvious.

The association between prevalence of *S. mansoni* infection and splenomegaly should be viewed with caution. Areas with a high prevalence of *S. mansoni* may also have a relatively high prevalence of malaria. This will cause an overestimation of the prevalence of splenomegaly caused by *S. mansoni* infection in communities with a high prevalence of *S. mansoni* infection.

The long development time of oesophageal varices (the cause of haematemesis) and ascitis and the high mortality make it difficult to estimate the association of prevalence of infection with late morbidity. Incidence estimates are probably more relevant for these pathologies as individuals have a significant chance of dying from exsanguation or liver failure, thus reducing the number of individuals with a haematemesis history or clinical ascitis found in cross-sectional community studies. It takes years to develop severe morbidity, therefore the relationship between the current prevalence of infection and the existence of late morbidity is not obvious. Perhaps field studies might not be the most appropriate type of study for obtaining data on late morbidity. Due to the relatively low prevalence of late morbidity, studies have to be larger than is usually the case. Also, a reported history of haematemesis might not be very reliable. Ongom et al. showed that reported history of haematemesis 'ever' was only twice as frequent as reported history of haematemesis 'this year' (Ongom and Bradley, 1972). This suggests either high mortality of individuals after an episode of haematemesis or recall bias. Also, it should be noted that it is not always clear if studies not reporting haematemesis or ascitis really did not find participants with this sign or symptom or simply did not measure late morbidity in their study.

Several study characteristics might influence the association between prevalence of infection and morbidity. We specifically examined the effect of age (children or adults). In individual studies it is difficult to disentangle the effect of age and the effect of intensity of

infection on prevalence of morbidity. Younger age groups tend to have a higher intensity of infection (Gryseels, 1988, Stelma *et al.*, 1993, Boisier *et al.*, 1995, Boisier *et al.*, 1998). And most studies show an association between intensity of infection and prevalence of morbidity (Gryseels and Nkulikyinka, 1990, Fulford *et al.*, 1991, Ndamba *et al.*, 1991, Kongs *et al.*, 1996, Kardorff *et al.*, 1997). In the current study we have separated the effect of age and intensity of infection by analysing the data for children and adults. The data did not indicate a different association for children and adults. Therefore, it is more likely that the difference in prevalence of morbidity between children and adults is caused by a difference in intensity of infection.

The presented associations between prevalence of *S. mansoni* infection and prevalence of morbidity and the estimates of prevalence of infection made by Brooker et al. (Brooker *et al.*, 2000b) will be used for re-calculating the Global Burden of Disease due to infection with *S. mansoni*. It must be noted that, given the non-linear character of the expression, it can only be used to make inferences on the community level. In case of predictions on the level of countries, it is necessary to consider heterogeneity in prevalences within the country.

Acknowledgements

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3

Diagnosis of early clinical consequences of *Schistosoma haematobium* infection: A novel approach to compare the performance of ultrasound and three methods for haematuria detection

Van der Werf, M. J. and De Vlas, S. J. Diagnosis of early clinical consequences of *Schistosoma haematobium* infection: A novel approach to compare the performance of ultrasound and three methods for haematuria detection. Submitted

Abstract

We compared the performance of four diagnostic methods to detect early clinical consequences of urinary schistosomiasis. We determined the associations between prevalence of *Schistosoma haematobium* infection and bladder pathology determined by means of ultrasonography or haematuria detected by reagent strip, questionnaire or visual examination, using published data from field studies.

After correction for morbidity due to other causes or misclassification, a consistent ratio in prevalence of haematuria of 3:2:1 resulted for reagent strip, questionnaire and visual examination. Ultrasound revealed markedly higher prevalences of bladder pathology in schools than in communities with the same prevalence of infection.

Our methodology offers an indirect comparison of diagnostic methods rarely used simultaneously. The simple and cheap questionnaire approach is not markedly inferior to the other techniques, making it the best option for field use. There are strong indications that ultrasound is less sensitive in adults, as compared to children with the same level of bladder pathology, implying a need for age-related cut-off values.

Introduction

Schistosoma haematobium, responsible for urinary schistosomiasis, is a highly prevalent parasitic infection affecting some 130 million individuals in over 40 endemic countries, predominantly in sub-Saharan Africa (Brooker *et al.*, 2000b, Chitsulo *et al.*, 2000). Humans are infected when they come into contact with water bodies inhabited by infected snails. The larval stages are transported to the liver where they mature. Adult *S. haematobium* worms live in the perivesical veins and start laying eggs after approximately 30 days. These eggs migrate through the bladder wall and are excreted with the urine. If an egg reaches fresh water, a larva is released that can infect the snail host, which closes the transmission cycle. Eggs that become trapped in the bladder wall give rise to pathological changes leading to blood in urine (haematuria), the main symptom of early *S. haematobium* infection (Mott *et al.*, 1983). After prolonged infection, the urinary system may be seriously affected, resulting in hydroureter, hydronephrosis and kidney failure (Jordan *et al.*, 1993, Chen and Mott, 1989). Since the Expert Committee meeting in 1984, WHO has aimed at schistosomiasis morbidity control, which became feasible after the introduction of praziquantel, an effective safe single dose drug (WHO, 1985, WHO, 1993). The drug can be delivered to infected individuals presenting at the health system or in community-based chemotherapy programmes, so that development of serious disease is prevented.

Identification of cases or communities for treatment (community diagnosis) is usually based on measuring infection by microscopic detection of eggs in urine. For example, Mali has adopted the WHO recommendations calling for mass treatment if the prevalence of infection in school children exceeds 50%, and for treatment of the group aged 5 to 19 at a prevalence between 20 and 50%. Below a 20% prevalence of infection, only children testing positive at screening receive treatment (WHO, 1993). Haematuria, indicative of early morbidity, may be a simpler and cheaper alternative for identifying communities in need of treatment (Lengeler *et al.*, 1991, Guyatt *et al.*, 1999a). Micro-haematuria can be detected by reagent strip testing. Macro-haematuria can be detected with the help of a questionnaire (i.e. asking individuals if they have experienced blood in urine in a given period) or by visual examination of a urine sample (Feldmeier and Poggensee, 1993). Since 1970, ultrasonography has been applied to visualise lesions in the bladder wall caused by trapped *S. haematobium* eggs (Degremont *et al.*, 1985, Burki *et al.*, 1986, Abdel-Wahab *et al.*, 1992b). This method is not suitable for large-scale use in control, but it is accepted as a relatively simple non-invasive method in hospital or research settings (Hatz *et al.*, 1992).

Many epidemiological studies have been conducted to investigate the characteristics of the above methods to measure early consequences of urinary schistosomiasis. This usually involved comparing the outcomes on morbidity/pathology with infection. The four methods enumerated above have rarely been directly compared. Moreover, most studies concerned a single school or community or neighbouring schools/communities in a defined area (district).

In this study, we aimed at evaluating the performance of four techniques for detecting early pathology or morbidity due to *S. haematobium* infection: bladder pathology by ultrasound, micro-haematuria by reagent strip and macro-haematuria by questionnaire or visual examination. We aggregated all field studies reporting prevalence of infection and pathology/morbidity. We explored the association of each of these methods with infection over different endemicity levels. Using these associations, we were able to make an indirect comparison of the performance of each of these four methods.

Methods

Data collection

We searched Pubmed (United States: National Library of Medicine) to identify all articles published up to the year 2002 reporting on the prevalence of ultrasonographically detectable bladder pathology, reagent strip detected micro-haematuria or macro-haematuria determined by questionnaire or by visual examination in unselected study populations (schools or whole communities) with known prevalence of *S. haematobium* infection. The references of the collected articles were checked for additional articles and quantitative information was extracted. Only pre-treatment data were included. Prevalence data from each community or school were included as independent observations, i.e. one study could contribute multiple observations to the analysis.

Data on bladder pathology were included if the pathology had been detected by ultrasound and was defined using the international standards (Cairo Working Group, 1992, Richter *et al.*, 1996), i.e. the presence of an 'irregular bladder wall', a 'bladder wall thickness > 5 mm', the 'presence of masses' or 'presence of pseudopolyps'. For micro-haematuria determined by reagent strip, we used the data reported for the 1+ positive limit. Data on macro-haematuria obtained by means of the questionnaire method were included if measured by asking participants to respond to a question such as 'Have you urinated blood during the past period' (the period varied between studies and a maximum of 4 weeks was chosen). We used the results reported for the longest period in analysing the one study that used two recall periods (1 day and 1 week) (Warren *et al.*, 1979). Prevalence studies on visibly detected macro-haematuria (inspection of urine samples by health workers) were included if they scored clearly red urine as positive. Only studies with prevalence of infection based on standard filtration of 10 ml urine or a method with comparable sensitivity were included: viz. filtration, centrifugation or sedimentation of 5 to 20 ml urine samples (Richards *et al.*, 1984).

Relating pathology or morbidity to infection

The curves describing prevalence of morbidity as a function of prevalence of infection start in the origin or a point higher on the *y*-axis (baseline level). This is because morbidity can also be due to another causes (e.g. micro-haematuria from bacterial urinary infection) or misclassification (e.g. brown concentrated urine can be reported as haematuria).

Detected haematuria not caused by *S. haematobium* infection was considered to be a false positive test result. The curves are assumed to remain horizontal at low prevalence of infection as only few or no cases have an infection intensity high enough to cause morbidity. For higher prevalences, the curves rise with increasing speed as the proportion with high intensity, associated with morbidity, will rise faster than the corresponding prevalence (Guyatt and Bundy, 1991). The curve eventually reaches its maximum level somewhere below 100%. This is because morbidity can be intermittent, or some of the infected individuals may not be susceptible for developing morbidity. Appendix 3A shows the mathematical equation used and the procedures to estimate its parameters.

Using the above equation, we assessed the associations between prevalence of *S. haematobium* infection and the four diagnostic methods: ultrasonographic detection of bladder pathology, micro-haematuria determined by reagent strip testing and macro-haematuria determined by questionnaire or by visual examination. We examined the impact of two determinants on these associations: study setting (school or community survey) and geographical area (West Africa: Benin, Burkina Faso, Gambia, Ghana, Ivory Coast, Mali, Niger, Nigeria, Senegal, Tchad; East Africa: Kenya, Madagascar, Mozambique, Tanzania, Zambia, Zimbabwe; and North Africa: Egypt, Ethiopia, Sudan). The fitted expressions corrected for the baseline level (i.e. not taking into account morbidity due to other causes) were used to study the pathology or morbidity caused by *S. haematobium* infection. Finally, we used the derived associations to compare the performance of the different diagnostic methods.

Results

We were able to make use of data from 19 studies containing information from 16 schools and 16 communities to estimate the association between prevalence of *S. haematobium* infection and bladder pathology by ultrasound (Heurtier *et al.*, 1986, Lamothe *et al.*, 1989, Abdel-Wahab *et al.*, 1992a, Dabo *et al.*, 1995b, Serieye *et al.*, 1996, Medhat *et al.*, 1997, Traoré *et al.*, 1998b, Delegue *et al.*, 1998, Subramanian *et al.*, 1999, Garba *et al.*, 1999, Hammam *et al.*, 2000b, Hammam *et al.*, 2000a, Gabr *et al.*, 2000, Habib *et al.*, 2000, El-Hawey *et al.*, 2000, Garba *et al.*, 2000, Champagne *et al.*, 2000, Abdel-Wahab *et al.*, 2000b, Campagne *et al.*, 2001). The prevalence of bladder pathology was clearly found to rise with the prevalence of infection (Figure 3.1a). Prevalences from school surveys were generally higher than from community surveys with a comparable prevalence of infection, as demonstrated by both a difference in baseline prevalence and a stronger association with infection. The calculated baseline prevalence was 13% for schools and 3% for community surveys. Apparently, schoolchildren have more bladder pathology due to other causes or are more often misclassified by ultrasound. The curves finally reached 79% for schoolchildren and 59% for communities. Pathology prevalences were somewhat higher in West Africa compared to North Africa (not shown), but this is partly explained by the fact that the latter mainly concerned community studies.

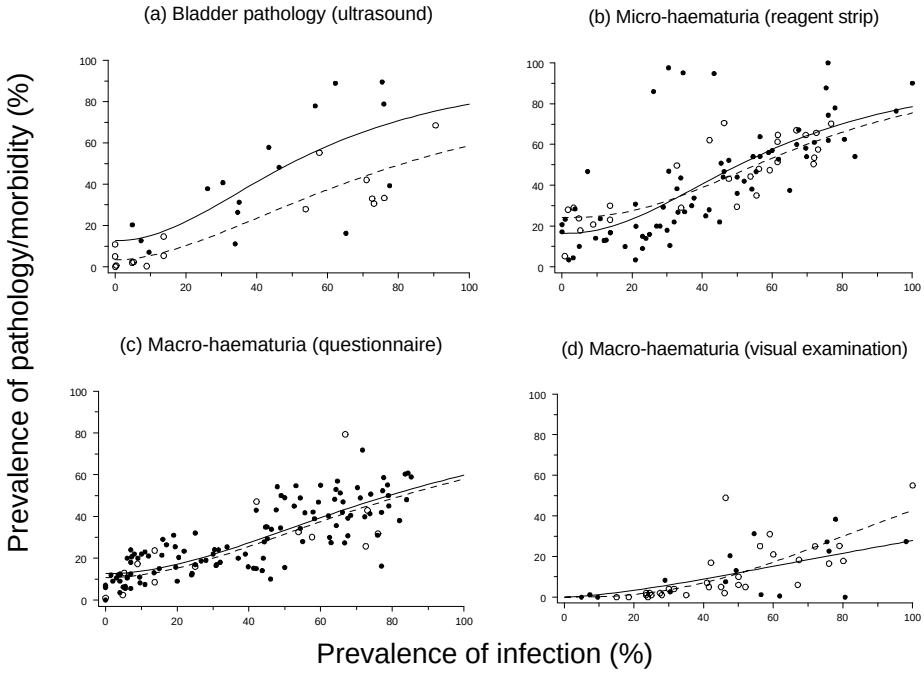

Figure 3.1: Observed associations between *Schistosoma haematobium* infection and early clinical consequences. Prevalence of (a) bladder pathology by ultrasound, (b) micro-haematuria by reagent strip, (c) macro-haematuria by questionnaire and (d) macro-haematuria by visual examination as a function of prevalence of *S. haematobium* infection. Observations come from published studies and concern schools (•) or whole communities (○). The curves are based on Equation 1 and represent schools (continuous line) or communities (dashed line). Parameters for bladder pathology are a = 0.13, b = 3.13 and c = 2.04 (schools) and a = 0.033, b = 1.35 and c = 1.78 (communities). Parameters for micro-haematuria detected by reagent strip testing are a = 0.16, b = 2.90 and c = 2.14 (schools) and a = 0.24, b = 2.09 and c = 2.37 (communities). Parameters for macro-haematuria detected by the questionnaire approach are a = 0.13, b = 1.17 and c = 1.91 (schools) and a = 0.11, b = 1.12 and c = 1.88 (communities). Parameters for macro-haematuria detected by visual examination are a = 0.00, b = 0.38 and c = 1.50 (schools) and a = 0.00, b = 0.75 and c = 2.50 (communities).

Data from forty-five studies comprising 74 schools and 28 communities was available to evaluate the prevalence of micro-haematuria detected by reagent strip testing (Wilkins *et al.*, 1979, Warren *et al.*, 1979, Sellin *et al.*, 1982, Mott *et al.*, 1983, Masaba *et al.*, 1983, Stephenson *et al.*, 1984, Mott *et al.*, 1985b, Sarda *et al.*, 1985a, Sarda *et al.*, 1985b, Ofori-Adjei *et al.*, 1986, Sarda, 1986, King *et al.*, 1988a, King *et al.*, 1988b, Gigase *et al.*, 1988, N'Goran *et al.*, 1989, Taylor *et al.*, 1990, Savioli *et al.*, 1990, Kiliku *et al.*, 1991, Prual *et al.*, 1992, Eltoum *et al.*, 1992, Abdel-Wahab *et al.*, 1992a, Bello and Edungbola, 1992, Kitange *et al.*, 1993, Jemaneh *et al.*, 1994, Mungomba and Kalumba, 1995, El-Sayed *et al.*, 1995, Nduka *et al.*, 1995, Birrie *et al.*, 1995, Mtasiwa *et al.*, 1996, Mafe, 1997, Lwambo *et al.*, 1997b, Ofoezie *et al.*, 1997, Traoré *et al.*, 1998b, Rasendramino *et al.*, 1998, Wamae and Lammie, 1998, Hall and Fentiman, 1999, Garba *et al.*, 1999, Hammam *et al.*, 2000a, Hammam *et al.*, 2000b, Gabr *et al.*, 2000, Garba *et al.*, 2000, Abdel-Wahab *et al.*, 2000b, Campagne *et al.*, 2001, Ndyomugyenyi and Minjas, 2001, Anosike *et al.*, 2001). Again, the

prevalence of haematuria increased markedly with the prevalence of infection (Figure 3.1b). Separate analysis for schools and communities showed a slightly lower baseline prevalence of micro-haematuria (reagent strip) for schools (24% vs. 16%); however, the curves largely overlapped and ultimately reached 77% for higher endemicity levels. The lower baseline prevalence for schools was mainly caused by one study contributing 25 observations to the analysis. The same study was also responsible for a slightly lower baseline prevalence rate in East Africa.

Twenty-one studies, comprising 117 schools and 14 communities, presented information on macro-haematuria that had been obtained by questionnaire (Warren *et al.*, 1979, Masaba *et al.*, 1983, Sarda *et al.*, 1985a, Lengeler *et al.*, 1991, Adom *et al.*, 1992, Eltoum *et al.*, 1992, Abdel-Wahab *et al.*, 1992a, Mungomba and Kalumba, 1995, Serieye *et al.*, 1996, Mtasiwa *et al.*, 1996, Mafe, 1997, Delegue *et al.*, 1998, Traquinho *et al.*, 1998, Traoré *et al.*, 1998b, Hatz *et al.*, 1998, Guyatt *et al.*, 1999a, Abdel-Wahab *et al.*, 2000b, Gabr *et al.*, 2000, Garba *et al.*, 2000, Hammam *et al.*, 2000a, Hammam *et al.*, 2000b, Ndyomugyenyi and Minjas, 2001). Schools and communities showed virtually identical associations of self-reported macro-haematuria rates with the prevalence of infection (Figure 3.1c). The fitted curves started at a baseline prevalence of about 12% and finally reached 60%. The majority of data points (80%) came from 2 studies in Tanzania (Lengeler *et al.*, 1991, Guyatt *et al.*, 1999a). These studies did not unduly influence the results, because curves separately fitted for each study did not markedly differ from each other, nor from that of the other 19 studies.

The association between prevalence of infection and macro-haematuria detected by visual examination was derived from 14 articles concerning 16 schools and 31 communities (Sellin *et al.*, 1982, Sarda *et al.*, 1985a, Sarda *et al.*, 1986, Sato *et al.*, 1988, Ozumba *et al.*, 1989, Eltoum *et al.*, 1992, Emejulu *et al.*, 1994, Mafe, 1997, Lwambo *et al.*, 1997b, Garba *et al.*, 2000, Campagne *et al.*, 2001, Garba *et al.*, 2001, Chippaux *et al.*, 2001, Ndyomugyenyi and Minjas, 2001). School surveys and community surveys with a low prevalence of *S. haematobium* infection reported no cases of macro-haematuria, yielding a baseline prevalence of 0.0% (Figure 3.1d). Overall, the prevalence of macro-haematuria by visual examination was markedly lower than for the other diagnostic methods. The curve for schools and communities initially overlapped and slightly diverged for higher prevalences. Geographical area nor study setting influenced the association between infection and visibly detected macro-haematuria.

The associations in Figure 3.1 between prevalence of infection and bladder pathology and haematuria were summarised (Figure 3.2a). As no significant difference was found between the curves for haematuria in schoolchildren and communities, these were combined ($p>0.20$ by co-variance analysis for all three methods). At all levels of infection, the prevalences estimated by each of the three methods did not vary in terms of order: micro-haematuria (detected by reagent strip screening) showed the highest prevalence, followed by macro-haematuria determined by questionnaire, and lastly, macro-haematuria detected by visual examination. After correcting for baseline, i.e. morbidity due to other causes (false positives), a proportional haematuria detection rate was found, corresponding

with a ratio of about 3:2:1 for these three methods over all prevalence of infection levels (Figure 3.2b).

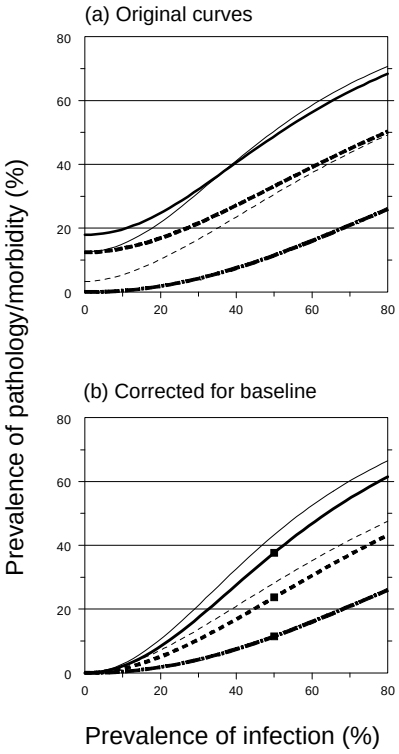

Figure 3.2: Predicted associations between *Schistosoma haematobium* infection and early clinical consequences. Summary of fitted curves from Figure 3.1 between prevalence of infection and prevalences of bladder pathology (thin lines), micro-haematuria by reagent strip (thick continuous line), and macro-haematuria by questionnaire (thick evenly dashed line) or visual examination of a urine sample (thick long-short dashed line), using the original curves (a) and after correction for baseline prevalence of morbidity or pathology due to other causes or misclassification (b). Separate curves are given for bladder pathology in schoolchildren (thin continuous line) and whole communities (thin dashed line) (see Figure 3.1 for parameter values). For haematuria combined curves are given, with parameters a = 0.18, b = 2.53 and c = 2.07 (reagent strip), a = 0.12, b = 1.17 and c = 1.90 (questionnaire), and a = 0.00, b = 0.56 and c = 2.11 (visual examination). At 50% prevalence of infection, the corresponding prevalences of haematuria corrected for baseline morbidity are indicated by the squares.

For example, at a 50% of infection level, the corresponding prevalence of haematuria due to *S. haematobium* infection was 38% for detection by reagent strip testing, 24% when using the questionnaire approach and 12% using the visual examination method. The associations of infection and bladder pathology for schools and communities were also proportional to those of haematuria, with bladder pathology in schoolchildren 15% above and bladder pathology in communities 25% below micro-haematuria. Hence, studies in

communities showed about 35% less bladder pathology due to *S. haematobium* than studies in schoolchildren with the same prevalence of infection (Figure 3.2b).

Discussion

It is reassuring to have been able to demonstrate that the four methods employed to detect early pathology or morbidity due to *S. haematobium* all showed a clear and consistent association with prevalence of infection. Also, in line will expectation, the prevalence of micro-haematuria determined by reagent strip testing was higher than that of macro-haematuria reported by questionnaire, which in turn was higher than the prevalence of visibly detected macro-haematuria. Furthermore, the fact that previous studies that explored associations between prevalence of infection and haematuria – measured by reagent strip (Jemaneh *et al.*, 1993, Lwambo *et al.*, 1997b), questionnaire (Lengeler *et al.*, 1991, Amali, 1994) or visual examination (Chippaux *et al.*, 2001) – found patterns similar to the current study, in which all available observations from the different field studies and geographical areas were aggregated, is convincing.

Our methodology offers a closer look at the performance of the different diagnostic techniques and their (biological) relation (Figure 3.2). The baseline levels (parameter *a* in the equation) of the estimated curves correspond to a "universal" proportion of false positives, i.e. those showing positive test results due to misclassification or other diseases/infections than *S. haematobium*. In our methodology, this proportion followed from studies in populations uninfected with *S. haematobium* or with low endemicity. We believe this to be superior to the common method of using the presence or absence of detected infection in individuals as a gold standard. In such studies, only a limited amount of urine (one to three repeated standard 10 ml urine filtrations (Murare and Taylor, 1987, N'Goran *et al.*, 1989, Kiliku *et al.*, 1991, Kitange *et al.*, 1993, El-Sayed *et al.*, 1995, Traquinho *et al.*, 1998, Guyatt *et al.*, 1999a, Garba *et al.*, 2000)) is usually used, so that many cases tend to go undiagnosed. This results in an overestimation of false positive test results and thus also in an underestimation of the specificity of the test (De Vlas and Gryseels, 1992). In our study, the specificity of the different diagnostic techniques simply follows from 100% – baseline prevalence: e.g. for haematuria, the specificity is respectively 82% for screening by reagent strip, 88% for the questionnaire method and 100% for the visual examination method. The sensitivity is unable to be directly determined by our methodology, as the number of individuals with blood in their urine due to *S. haematobium* infection that goes undetected is unknown (false negatives). However, the proportional differences between the curves in Figure 3.2b provide some indication of how many cases are at least missed by the respective techniques.

We assumed that the baseline prevalences do not depend on endemicity. This may be an oversimplification, as infectious diseases tend to cluster (Booth *et al.*, 1998a). For example, the risk of both schistosomiasis and urinary infection (also responsible for haematuria) will probably be higher in environments with no sanitary facilities available. Also, individuals living in the poorest rural areas are likely to have nutritional deficiencies, making them

more susceptible to any disease. While the clustering of disease may have resulted in somewhat steeper lines, the relation between the different curves will not have been seriously affected. The proportion of false positive test results due to misclassification is not likely to be associated with the prevalence of schistosome infection.

After correcting for false positives, the prevalence of ultrasound detected pathology in schoolchildren appeared to be largely parallel (always about 10% lower) to that of infection. As stated above, many infected cases are missed by standard parasitological screening and are not included in the prevalence of infection. Therefore, more than a fixed 10% of the children will be infected with *S. haematobium* infection but will have no ultrasound detectable pathology. Nevertheless, a 10% prevalence of (detected) infection means that hardly any cases with an infection intensity high enough to show *S. haematobium*-related pathology will occur, whereas an 80% prevalence of infection (and a probable 100% infection rate) causes this percentage to rise to 70%. This clearly demonstrates the impact of increasing intensity of infection (and risk of developing disease) with increasing prevalence of infection.

Surprisingly, the prevalence of bladder pathology measured by ultrasonography was considerably lower in communities than in schoolchildren with the same prevalence of infection. Children showed both more false positive results (higher baseline prevalence in Figure 3.2a) and a stronger association with infection (Figure 3.2b). The difference between adults and children are in actual fact likely to be even larger, as community observations also include children. Assuming that children make up 50% of a community, the curve for communities is expected to be located somewhere halfway between schoolchildren and adults. The large difference in baseline prevalence for schoolchildren (13%) and communities (3%) would appear to suggest that false positive ultrasound results do not occur in adults. However, the baseline level for communities was disproportionately determined by six observations from a series of publications from one study in Egypt (Hammam *et al.*, 2000a, Hammam *et al.*, 2000b, Gabr *et al.*, 2000, Abdel-Wahab *et al.*, 2000b, El-Hawey *et al.*, 2000, Habib *et al.*, 2000). This extensive study, which reported relatively low prevalences of bladder pathology (possibly due to a very good quality control) in low endemic situations, may have resulted in some underestimation of the rate of false positives, but it could only account for half of the difference between studies on children and communities. Thus, misclassification or false positive results due to other diseases such as urinary tract infections and urethral stenosis seem to be substantially more prevalent in children than adults. It is not clear why this should be the case.

Our finding that about 35% less *S. haematobium*-related bladder pathology was found in community studies than in studies in schoolchildren, given the same prevalence of infection, may also have been subject to bias, in particular as the number of observations was rather low. However, in moderate to high endemic areas, almost consistently lower prevalences were seen in community studies than in studies on schoolchildren (Figure 3.1a). Other studies corroborate the finding that lower rates of ultrasonographically

detected bladder pathology are seen in adults than in children. In the four studies where observations for children and adults were reported separately (Heurtier *et al.*, 1986, Lamothe *et al.*, 1989, Serieye *et al.*, 1996, Traoré *et al.*, 1998b), prevalences of pathology in children were always considerably higher than in adults, even after correction for false positives and the difference in prevalence of infection. Moreover, the study by Heurtier (Heurtier *et al.*, 1986), which was the only one that presented prevalences of bladder pathology for different ages and egg count groups, reported a prevalence of 77% in 70 children with 1-99 eggs/10 ml urine, versus only 62% in 68 adults of the same egg count group ($p = 0.05$). The difference in presence of (ultrasound detected) bladder pathology between children and adults could be explained by a more potent immune response in children. However, our results on haematuria were very consistent in showing equal levels of morbidity for children and communities (and thus adults). As haematuria results from the same mechanism, i.e. bladder lesions from eggs that get trapped in the bladder mucosa (Mott *et al.*, 1983, Hatz *et al.*, 1998), we would expect equal levels of pathology for children and adults with the same prevalence of infection. Thus, the most plausible explanation is that ultrasound leaves a considerable number of adults with bladder pathology undetected. Apart from those with *S. haematobium*-related bladder pathology, this could also concern cases with pathology from other diseases (false positives). One explanation would be that the internationally agreed standards to define bladder pathology by ultrasound (Cairo Working Group, 1992, Richter *et al.*, 1996) cannot simply be used irrespective of age. Separate criteria for children and adults should be developed.

In accordance with the general characteristics of the three methods used to detect haematuria, reagent strip testing had a higher baseline prevalence and stronger association with infection compared to macro-haematuria established by the questionnaire approach, and by visual examination. In the first place, occult blood in urine can be detected with the help of reagent strips (high sensitivity for detection of haematuria, i.e. > 5 erythrocytes/µl (Bee *et al.*, 1979, Kaiser *et al.*, 1992)), yet will not be reported nor detected by visual examination. The latter methods are thought to select cases with relatively heavy infection and more severe pathology (Lwambo *et al.*, 1997b). Secondly, haematuria due to *S. haematobium* infection is transitory (Jordan *et al.*, 1993, Chen and Mott, 1989), implying that macro-haematuria has a higher chance of being detected via the questionnaire method than after the visual examination of a single urine sample. Given a detection ratio of 2:1 (Figure 3.2b), at least 50% of macro-haematuria cases will be missed when relying solely on a visual examination. All cases with macro-haematuria detected by either visual examination or questionnaires that are truly attributable to *S. haematobium* infection will in all likelihood yield a positive reagent strip test. It is therefore not likely that questionnaires or visual examination of a urine sample will add to the information derived from the reagent strip results. The one study that presented individual results by reagent strip and questionnaire revealed that only 10 individuals of the 133 who had negative reagent strip tests reported having haematuria (Mtasiwa *et al.*, 1996). This small proportion (7.5%) can easily be explained by the rate of false positives that resulted from our study. False reports

of blood in urine easily result, especially when brownish-coloured concentrated urine is mistaken for blood, a mistake which is far less likely to occur during visual examination of a urine sample, a procedure which is normally performed by a trained health worker. On the other hand, the questionnaire method may also underdiagnose haematuria, as individuals may consider blood in urine as a venereal disease and feel ashamed (Amazigo *et al.*, 1997), or forget recent episodes of haematuria, especially in areas where blood in urine is not considered a problem (Taylor *et al.*, 1987, Aryeetey *et al.*, 1999). However, in the light of the fact that 50% more truly positive cases are detected by reagent strip screening (given the ratio of 3:2 in Figure 3.2b), most of which will not have gross haematuria, this underdiagnosis is not expected to pose problems. Regarding the possibility of recall bias, it is also interesting to note that length of the recall period used in the studies included (usually 2 or 4 weeks) proved to be of no importance (Van der Werf *et al.*, in press-c). The proportion of positive reagent strips not attributable to *S. haematobium* is even higher than the proportion false positives by questionnaire. This is because other (medical) causes such as urinary tract infections, sexually transmitted diseases and menstruation mainly result in very small quantities of blood in urine, usually not visible to the eye. These causes may be more prevalent in adults than in children (Mohr *et al.*, 1986, Dodge *et al.*, 1976), thereby explaining the difference in baseline levels between communities and schoolchildren (24% vs. 16%). However, this difference is not significant and disappears at higher endemicity levels (prevalence of infection >20%). Ultimately, in choosing between the three methods for detecting haematuria, the objectives of the research or control programme and the resources available are decisive. Many false positive outcomes will lead to unnecessary treatment of cases with no (or low) infections and consequently high drug cost, whereas many false negatives will limit the effect of the intervention. The questionnaire method may sometimes be favourable, as it requires fewer materials and personnel training than does the use of reagent strips or the visual examination approach.

We were also able to evaluate the performance of the three haematuria detection techniques for categorising communities in the WHO recommended treatment strategies (WHO, 1993) with the help of our database. The performance of haematuria for identifying communities below or above the cut-off values of 20% and 50% prevalence of *S. haematobium* infection was comparable between the three methods (Appendix 3B). About 50% to 80% of communities and schools would remain in the same category as when using the WHO recommended cut-off values based on infection. Only three schools would be seriously misclassified by visual examination of a urine sample, i.e. no treatment instead of mass treatment of the entire population. Given the practical advantages of the questionnaire method, we consider it the best alternative to infection for cheap and simple identification of communities in need of treatment.

In conclusion, (1) the detection methods for early clinical pathology and morbidity show marked associations with prevalence of *S. haematobium* infection, (2) ultrasound detects fewer cases with bladder pathology in adults compared to children with the same degree of pathology, (3) after correction for false positives, prevalences of haematuria due to *S.*

haematobium are almost proportional, with a ratio of reagent strip : questionnaire : visual examination of 3:2:1, (4) as the questionnaire method does not have test characteristics markedly inferior to the other diagnostic techniques, its advantage in terms of required cost, time and personnel will usually make it the method of choice for both individual and community diagnosis, (5) our methodology can also be applied for other infectious diseases, particularly those in which development of disease depends on the intensity of infection.

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APPENDIX 3A

For a given school or community, we assume a prevalence (%) of pathology or morbidity Y to be a function of prevalence (%) of infection X according to

$$Y/100 = (a + b\,(X/100)^{c})/(1 + b\,(X/100)^{c})$$

with baseline parameter a ($0 \leq a < 1$) and shape parameters b ($b > 0$) and c ($c > 1$). The equation has a first derivative which equals zero at $X = 0\%$ and $Y = a \cdot 100\%$. This guarantees that at very low prevalences of infection, no or only limited detectable morbidity is assumed to be due to *Schistosoma haematobium*. $Y = a \cdot 100\%$ is the baseline prevalence of pathology or morbidity, i.e. pathology or morbidity caused by misclassification or other diseases (false positives). The curve rises monotonously and finally reaches a prevalence of morbidity below $Y = 100\%$. By taking parameter $a = 0$ (no baseline), the equation represents morbidity due to *S. haematobium* infection, corrected for morbidity due to other causes. Further details are described in Van der Werf *et al.* (2002) (Van der Werf *et al.*, 2002a, Van der Werf *et al.*, in press-b).

We used Systat (version 3.0, 1986) to estimate the values of parameters a, b and c by fitting the equation to all n observations. The fit was determined by assuming a binomial distribution for each observation i ($i = 1, \ldots, n$), without assigning weight according to size of the population. The latter assumption can easily be made, since the vertical location is determined by many more phenomena (e.g. the community base-line morbidity) than the size of the population alone. The number of individuals comprising one observation was usually about 100, with a minimum of 32. To explore potential bias due to overrepresentation of large studies (contributing many observations), we have re-analysed all associations with attributing weight to observations according to the reciprocal of the square root of the number of observations coming from each study. For instance, observations from a study contributing 16 schools or communities had a weight of 1/4 compared to observations coming from studies contributing one school or community. This approach did not lead to significantly different results and we therefore only reported the standard procedure based on associations without attributing weight according to study size.

Some adjustments were necessary to apply our methodology. For micro-haematuria detected by reagent strip (association for community) and macro-haematuria detected by questionnaire, fitting the Equation yielded a biologically unrealistic curve indicated by a sharp increase of morbidity at low prevalence of infection and a point of inflexion at prevalence of infection $X < 25\%$. For both situations, we reduced the number of parameters by pre-setting the point of inflection at prevalence of infection $X = 50\%$, which corresponds to $b = ((c - 1)/(c + 1))\ 2^{c}$. One study (Okoli and Odaibo, 1999) with many outlier observations and one outlier observation from (Lengeler *et al.*, 1991)

(prevalence of *S. haematobium* infection 23% and prevalence of macro-haematuria by questionnaire 64%) were excluded from the analysis.

APPENDIX 3B

The World Health Organization (WHO) recommends no treatment (apart from those found positive at the screening) if the prevalence of *Schistosoma haematobium* infection ≤20%, mass treatment of the 5 to 19 year age group (20 – 50%), and mass treatment of the whole community (>50%) (WHO, 1993). The prevalence of haematuria may provide a better (rapid, simple and cheap) method for community diagnosis (Lengeler *et al.*, 2002). Some have used the same cut-off levels of 20% and 50% for haematuria by reagent strip (Hopkins *et al.*, 2002). It may be better to use cut-off prevalences corresponding to the values for infection. From Figure 3.2a, it follows that these prevalences are 25% and 49% for reagent strip, 17% and 33% for questionnaire, and 2% and 12% for visual examination.

For each data point (community or school) in our database, we assessed whether the same treatment strategy would follow from using cut-off levels for haematuria compared to infection. To prevent dependency, the cut-off levels for haematuria for each data point were determined after re-fitting the curves of Figure 3.2a excluding this data point. Table 3.1 shows the proportion of schools and communities correctly categorised for all three methods detecting haematuria.

Table 3.1: Recommended treatment strategy based on prevalence of haematuria. Values indicate the proportion of schools and communities that would be correctly categorised using cut-off prevalences for haematuria instead of the WHO recommended prevalence categories for Schistosoma haematobium infection. No treatment (apart from those found positive at the screening) if the prevalence of infection ≤20%, mass treatment of the 5 to 19 year age group (20 – 50%), and mass treatment of the whole community (>50%) (WHO, 1993). Cut-off prevalences for haematuria corresponding to 20% and 50% infection from Figure 3.2a were 25% and 49% for reagent strips, 17% and 33% for questionnaires and 2% and 12% for visual examination, respectively.

Haematuria test	No treatment	Mass treatment of 5 to 19 year age group	Mass treatment of whole community
Reagent strips	78 (61–95)	46 (30–63)	79 (66–92)
Questionnaire	64 (50–78)	47 (32–62)	78 (66–90)
Visual examination	100 (48–100)	61 (41–81)	74 (54–94)

The overall performance of the three methods did not significantly differ ($p > 0.3$ by Chi-square test). Only for visual examination of a urine sample, a number of schools (3) would be seriously misclassified, i.e. receiving no treatment instead of mass treatment of the whole community.

4

No effect of recall period length on prevalence of self-reported haematuria in *Schistosoma haematobium* endemic areas

Van der Werf, M. J., Borsboom, G. J. J. M. and De Vlas, S. J. No effect of recall period length on prevalence of self-reported haematuria in *Schistosoma haematobium* endemic areas. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, in press

Haematuria, the main early symptom of urinary schistosomiasis, due to *Schistosoma haematobium* infection, is frequently measured by questionnaire (i.e. by asking individuals if they have had blood in their urine). Commonly, a period of 2 to 4 weeks is used. This method enables rapid - and relatively inexpensive - identification of communities for mass treatment of this important parasitic disease, and is recommended by WHO (Lengeler *et al.*, 2002, WHO, 2002). Several studies have shown that prevalence of self-reported haematuria is a convenient proxy for prevalence of infection (Lengeler *et al.*, 1991, Guyatt *et al.*, 1999a).

In retrospective questionnaire surveys of medical events, recall bias is one of the factors that may affect outcomes. Especially for less significant events (such as haematuria), frequency, duration and meaningfulness of the event may contribute to recall (Coughlin, 1990). Furthermore, as haematuria is intermittent, prevalence of reported haematuria is expected to increase with duration of recall period. It is important to assess the effect of recall period length on the prevalence of reported haematuria. Only two studies used different recall periods. Adom *et al.* (1992) reported a higher prevalence for haematuria "ever" compared to current haematuria. The other study showed inconsistent results as the prevalence for last week was lower then that for the last 24 hours (Warren *et al.*, 1979). We aimed to assess the effect of recall period length on the association between prevalence of reported haematuria and *S. haematobium* infection using data from field studies with different and also more commonly applied recall periods.

We collected all articles published before 2002 that reported prevalence of haematuria measured by questionnaire with a maximum recall period of 4 weeks and prevalence of *S. haematobium* infection in unselected, untreated study populations in Africa. Prevalence of infection had to be based on standard filtration of a 10 ml urine sample or a method with comparable sensitivity: viz. filtration, centrifugation or sedimentation of 5 to 20 ml urine samples. Twenty-one studies were included in a meta-analysis, concerning 117 schools (10 studies) and 14 communities (11 studies); 10 studies were performed in East, 6 in North and 5 in West Africa. Every community or school was included as one observation in the analysis, so one study could contribute several observations. Recall periods in the included studies were 1 day, 1 week, 2 weeks, and 4 weeks, represented by 1, 2, 53 and 58 observations, respectively. For 17 data points, the period was not specified. The impact of recall period length, study setting (school vs. community) and geographical location (East Africa vs. North and West Africa) on prevalence of haematuria was examined by analysis of covariance, using prevalence of infection as covariate.

A wide range of endemicity levels was present, as the prevalences of *S. haematobium* infection varied from 0 to 85 percent (Figure 4.1). There was a strong positive association ($r = 0.81$; $p<0.0001$) between prevalence of infection and reported haematuria in the total data set. No significant main effect of recall period length on prevalence of haematuria was found ($p = 0.40$), nor a significant interaction effect between recall period length and prevalence of infection ($p = 0.12$). This implies that the relation between prevalence of haematuria and infection did not differ between the four recall periods. Furthermore, there

were no significant effects of geographical location (p = 0.48) and study setting (p = 0.91), the latter of which can be considered a proxy for age. The final model for prevalence of haematuria only contained prevalence of infection, having a regression line with slope 0.51 (95% C.I.: 0.44 - 0.58) and intercept 8.7 (95% C.I.: 5.6 - 11.8). The small intercept represents misclassification or haematuria from other diseases. The great majority of data points (80%) came from 2 studies in Tanzania. These studies did not unduly influence the results, because their regression lines did not differ significantly from each other, nor from that of the other 19 studies combined.

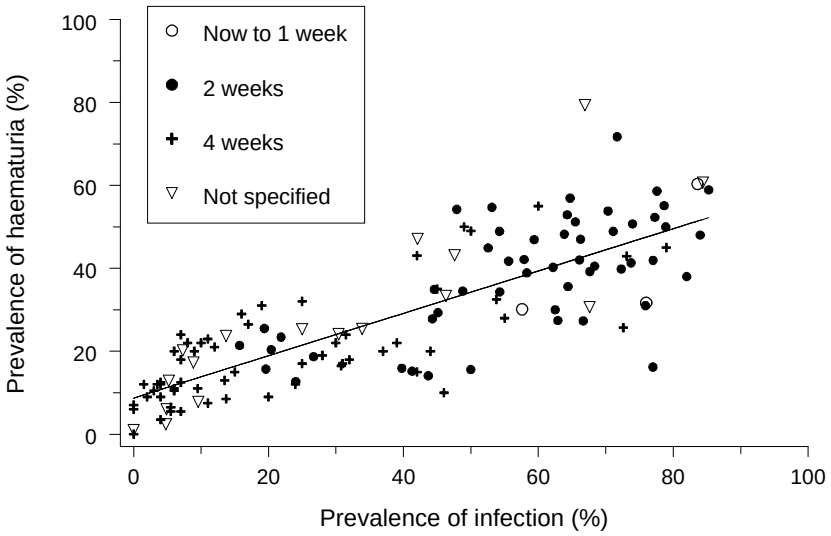

Figure 4.1: Association between prevalence of *Schistosoma haematobium* infection and reported haematuria for different recall periods. Every point represents one school or community. The regression line is $y = 8.7 + 0.51\,x$, with 65% of the variance explained. Sources of data are reported in "Morbidity and infection with schistosomes or soil-transmitted helminths" by M.J. Van der Werf & S.J. De Vlas (report at the request of WHO/PVC/CPE).

Testing the effect of recall period length on reported haematuria would ideally be done in an experimental context. However, we believe that the evidence of no effect of recall period length on the association between prevalence of haematuria and *S. haematobium* infection, as shown in our study using literature data, is convincing. This finding can be explained by the possibility that intervals between consecutive episodes of haematuria are short (days) compared to the recall periods (weeks). Also, potential effects of recall period length may be neutralised by two possible mechanisms. First, memory decay (failure to remember the event) may have caused underreporting of haematuria that ended between 2 and 4 weeks ago, as haematuria is often not regarded a serious symptom in endemic areas. Second, reporting events that occurred outside the recall period (telescoping) might have been more important for the shortest recall periods.

Earlier studies have shown that prevalence of haematuria by questionnaire provides a simple and adequate method for community diagnosis due to its strong association with prevalence of infection. It is reassuring that this association is consistent for different studies as shown in our meta-analysis. The choice of recall period (2 or 4 weeks) proves to be of minor importance. This is of operational importance for community treatment programmes and strengthens the case for using questionnaires as a simpler, cheaper alternative to urine examination.

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5

Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa

Van der Werf, M. J., De Vlas, S. J., Brooker, S., Looman, C. W. N, Nagelkerke, N. J. D., Habbema, J. D. F. and Engels, D. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Tropica*, in press

Abstract

Health policy making in developing countries requires estimates of the (global) burden of disease. At present, most of the available data on schistosomiasis is limited to numbers of individuals harbouring the infection. We explored the relationship between the presence of schistosome infection and clinical morbidity, in order to estimate numbers of individuals with disease-specific morbidity for *Schistosoma haematobium* and *S. mansoni* infection in sub-Saharan Africa.

We searched the literature for cross-sectional data from field studies reporting both schistosome infection and morbidity. This was used to derive a functional relationship between morbidity and infection. After standardisation for diagnostic method, the number of individuals with specific types of clinical morbidity or pathology was predicted. As only aggregated prevalences of infection were available for countries or areas, we adjusted for heterogeneity in infection levels within communities in those countries.

In total, 70 million individuals out of 682 million (2000 estimate) in sub-Saharan Africa were estimated to experience haematuria in the last 2 weeks associated with *S. haematobium* infection, and 32 million dysuria. Ultrasound detected serious consequences of *S. haematobium*, major bladder wall pathology and major hydronephrosis, were predicted at 18 and 10 million, respectively. Infection with *S. mansoni* was estimated to cause diarrhoea in 0.78 million individuals, blood in stool in 4.4 million and hepatomegaly in 8.5 million. As the associations between prevalence of *S. mansoni* infection and prevalence of diarrhoea and blood in stool were not very clear, the resulting estimates may be underestimations. Using the very limited data available, we estimated the mortality rates due to non-functioning kidney (from *S. haematobium*) and haematemesis (from *S. mansoni*) at 150,000 and 130,000 per year.

Given the overall high number of cases with schistosomiasis-related disease and associated death, we conclude that schistosomiasis remains an important public health problem in sub-Saharan Africa.

Introduction

Health policy in developing countries is based on targeting diseases with high preventable burdens of disease. This requires estimates on the (global) burden of disease. Currently WHO estimates the burden of schistosomiasis on the basis of the number of individuals infected with *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum* (Murray and Lopez, 1996), with an associated low disability weight (0.005 compared to 0.172 for a malaria episode). However, not all infected individuals experience morbidity. Also, not all individuals with schistosomiasis-related disease are found positive at standard screening (De Vlas and Gryseels, 1992, Utzinger *et al.*, 2001). Thus, estimates of the prevalence of morbidity are needed. Disability weights can then be assigned to symptoms to calculate the burden of disease, as is done for many other diseases in the burden of disease calculation (Murray and Lopez, 1997a).

Often, epidemiological surveys only report the prevalence of schistosome infection (Brooker *et al.*, 2000b, Chitsulo *et al.*, 2000). Attempts to estimate the prevalence of specific symptoms from the prevalence of infection concluded that 20 million have serious clinical disease and 120 million are symptomatic, by using the well-known figure of 200 million infected individuals and assuming proportions of 10% and 60% for serious clinical disease and being symptomatic, respectively (WHO, 1993, Crompton, 1999, Savioli *et al.*, 1997). Others assumed that intensity of infection is associated with morbidity and related the prevalence of morbidity in a population to intensity of infection (Chan *et al.*, 1996, Gryseels and Polderman, 1991, Medley and Bundy, 1996). However, there is a dearth of data on intensity of infection, making it necessary to infer intensity from statistical associations between prevalence and intensity of infection (Guyatt and Bundy, 1991). Still others estimated morbidity due to helminth infection, by assuming a threshold value for the number of worms above which morbidity occurs (Chan *et al.*, 1994, De Silva *et al.*, 1997). These studies ignored that most symptoms and signs caused by helminth infection are non-specific (e.g. anaemia due to malaria infection and bloody diarrhoea due to amoebic dysentery).

This paper attempts to predict the number of individuals with morbidity associated with schistosome infection to serve as input for the Global Burden of schistosomiasis calculations. Since most accessible data are available for *S. haematobium* and *S. mansoni* infection and the majority of the individuals infected with schistosomes live in sub-Saharan Africa (165 million vs. 28 million in the rest of the world (Chitsulo *et al.*, 2000)), we focussed on *S. haematobium* and *S. mansoni* infections in sub-Saharan Africa. We investigated the relationship between the presence of schistosome infection and clinical morbidity (or pathology) by using all published field studies. The parasitological data were standardised for differences in diagnostic sensitivity, we accounted for non-specific morbidity, and we adjusted our estimates for heterogeneity in infection.

Methods

In order to arrive at an estimate of the number of clinical cases from the prevalence of infection in a country, the following points were considered: (1) schistosomiasis causes many different signs and symptoms, out of which a selection had to be made; (2) morbidity is concentrated in individuals with current (or past) high intensity of infection; (3) most clinical morbidity associated with schistosomiasis is non specific; (4) prevalence of infection data were available on an aggregated level (country), but schistosomiasis occurs focally and, therefore, heterogeneity in the degree of endemicity among communities has to be accounted for; (5) the predictions are affected by uncertainty in assumptions and empirical data.

Identification of signs and symptoms of schistosome infection

A list of all signs and symptoms caused by infection with *S. haematobium* and *S. mansoni* was prepared from the literature (Chen and Mott, 1988, Chen and Mott, 1989, Jordan *et al.*, 1993) and expert advice. Our analysis was restricted to signs and symptoms for which information on both prevalence of infection and morbidity or pathology was available from field studies in populations unselected for infection status, disease or other criteria. The following signs and symptoms, probably related to infection with *S. haematobium* or *S. mansoni*, were excluded from analysis due to insufficient data. For both *S. haematobium* and *S. mansoni*: cercarial dermatitis, pneumonia at invasion stage, anaemia, and ectopic lesions. For *S. haematobium*: bladder cancer, genital lesions, and renal failure. For *S. mansoni*: Katayama fever, liver failure and cor pulmonale. For more subtle health effects evidence was conflicting: reduction of growth (Abdel-Salam and Abdel-Fattah, 1977, Ekanem *et al.*, 1994, Forsyth and Bradley, 1964), impaired cognitive development (Kvalsvig, 1988, Nokes and Bundy, 1994) and reduced physical fitness (Kvalsvig, 1986, Stephenson *et al.*, 1985).

Associating prevalence of infection and prevalence of morbidity/pathology

Pubmed (National Library of Medicine, United States) was searched for field studies in unselected study populations on *S. haematobium* and/or *S. mansoni* infection and morbidity. The references in collected articles were searched for additional articles and quantitative information was extracted. As prevalence data from each reported community or school were included as independent data points, one study could contribute several data points to the analysis.

In all identified field studies, the prevalence of *S. mansoni* infection was assessed by stool sample examination. Quantity of stool (number of stools × number of samples per stool × weight per sample) differed among studies (range 25 mg – 300 mg) and this affected the reported prevalence of infection. Using an existing egg count model (De Vlas *et al.*, 1992), we standardised *S. mansoni* prevalences to those of a default diagnostic technique (i.e. a single 41.7 mg Kato-Katz faecal sample) to be able to compare prevalences obtained by the examination of different quantities of stool (Van der Werf *et al.*, 2002a). *S. haematobium*

prevalences were all determined by examining 10 ml urine samples with the standard filtration technique. Therefore, standardisation was not necessary.

Various methods have been used for measuring morbidity and pathology, e.g. questionnaire, inspection of urine or stool sample, haemasticks, clinical examination and ultrasound. We decided to use questionnaire data on haematuria and dysuria for *S. haematobium* infection, and questionnaire data on diarrhoea, blood in stool, abdominal pain and haematemesis for *S. mansoni* infection. If morbidity was reported for more than one recall period we used the recall period closest to 2 weeks. Data for hepatomegaly, splenomegaly and ascitis were obtained from studies that used clinical examination. For hepatomegaly we used data from studies reporting prevalence measured at mid-sternal level (MSL) as it is thought to be more related to infection with intestinal schistosomes than measurements at mid-clavicular level (MCL). Minor bladder wall pathology prevalences were included if the pathology had been detected by ultrasound and was defined as presence of at least 'irregular bladder wall', 'bladder wall thickness > 5 mm', 'presence of masses', or 'presence of pseudopolyps' and major bladder wall pathology had to be defined as presence of at least 'bladder wall thickness > 10 mm' or 'several localised hypertrophies'. Hydronephrosis data were included if detected by ultrasound and defined as marked pyelocalyceal dilatation (moderate hydronephrosis) or marked reduction of functional parenchym (major hydronephrosis).

From these data, we tried to determine the relation between community prevalences of infection and prevalences of each type of morbidity (or pathology), assuming a three parameter (*a*, *b*, and *c*) non-linear mathematical relationship (Appendix 5A). This equation allows for a baseline morbidity defined by parameter *a* (prevalence due to other diseases), has zero derivative at $x = 0$ and $y = a$ (i.e. no morbidity due to schistosome infection at very low prevalences) and asymptotically (but not necessarily) reaches a prevalence of morbidity of 100%. Due to the convex association between prevalence of infection and prevalence of morbidity, communities with relatively high infection prevalences contribute disproportionately to the burden of morbidity.

Predicting the number of individuals with morbidity

Using the above quantitative relationship, prevalence of morbidity can be calculated from available data on the prevalence of infection in areas of sub-Saharan Africa. Prevalences of infection data were provided by an international initiative launched by WHO and its partner at Imperial College, London, which attempted to collate the available schistosomiasis survey data from both published and unpublished sources (see Brooker *et al.*, 2000a for inclusion criteria and further details). As most available data are on school-aged prevalence, prevalence of infection in pre-school children and adults was estimated from data on school children using species-specific regression models (Guyatt *et al.*, 1999b), thereby providing a more reliable estimate of total numbers infected (Brooker *et al.*, 2000a). In areas without comprehensive survey data, estimates of infection prevalence were made using models of the distribution of infection in relation to environmental

variables (Brooker *et al.*, 2002), and were counterchecked with other information (Doumenge *et al.*, 1987) and expert opinion. This provided prevalence data of schistosomiasis in defined at risk populations in sub-Saharan Africa (Africa except Algeria, Egypt, Eritrea, Libya, Morocco, Tunisia and Western Sahara).

As prevalence data were not available on the community level, we had to estimate the geographical heterogeneity in the prevalence of infection for communities at a given mean prevalence of infection in an area/country. A normal distribution of logit transformed prevalence data appeared to provide an adequate description of this heterogeneity (Appendix 5B). The number of individuals with morbidity was calculated by multiplying the mean estimated prevalence of morbidity with the at risk population in a country/region. Estimates of morbidity and pathology (haematuria, dysuria, bladder pathology, hydronephrosis, diarrhoea, blood in stool, hepatomegaly and splenomegaly) were calculated as described above for pre-school children, schoolchildren and adults, separately. Estimates for major hydronephrosis were assumed to apply to schoolchildren and adults only; the possible cases among pre-school children were neglected. The number of individuals with moderate hydronephrosis was calculated by subtracting the number of individuals with major hydronephrosis from the number of individuals with both moderate and major hydronephrosis. Numbers of other chronic morbidity (ascitis and haematemesis) were attributed to adults only.

To estimate 90% confidence intervals for the number of individuals with morbidity in sub-Saharan Africa, we used bootstrapping (Efron and Tibshirani, 1993). This is a generally applicable way for constructing confidence intervals where in a series of replica data sets are created by drawing samples from the original set of data points. The new data sets have the same size as the original data set and are drawn with replacement. In this way the replication of the sampling procedure is mimicked and the distribution of the number of individuals as based on each replica represents what would have happened if we had re-conducted the data sampling hundreds of times. This procedure gives confidence intervals in situations where analytical solutions are not possible, i.e. in this situation where we could not formulate the model as a generalised linear model. In our study, we generated 200 bootstrap samples for each type of schistosomiasis related morbidity. Then we calculated the parameters a, b and c for each bootstrap sample and predicted the number of individuals with morbidity as described in Appendix 5B. The 200 estimates of the number of individuals with morbidity were ranked and the 10^{th} and 190^{th} were selected to represent the 90% confidence interval. Intervals could be calculated for haematuria, dysuria, bladder pathology, diarrhoea and blood in stool. Calculation of intervals occasionally failed because the association between prevalence of infection and morbidity was not very distinct (e.g. hepatomegaly) or because of too few data points (e.g. haematemesis). The 90% confidence intervals only take into account the uncertainty in the curve parameters a, b and c.

The number of individuals with morbidity or pathology associated with *S. haematobium* and *S. mansoni* were estimated for Angola, Benin, Botswana, Burkina Faso, Burundi,

Cameroon, Central African Republic, Chad, Côte d'Ivoire, DR Congo, Ethiopia, Gambia, Ghana, Guinea, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe. No estimates of *S. mansoni* associated morbidity were provided for Congo, Equatorial Guinea, Eritrea, Gabon, Guinea-Bissau and Somalia, as this infection was non or very low endemic (prevalence ~ 0.0). Similarly, estimates of *S. haematobium* associated morbidity were not calculated for Burundi, Equatorial Guinea, Eritrea and Rwanda.

Mortality

Mortality caused by infection with *S. haematobium* will mainly be due to kidney failure and bladder cancer. Mortality due to *S. mansoni* infection will be caused by haematemesis or liver failure. As few studies report the prevalences of these conditions or their mortality rate, our estimates of incidence and mortality due to kidney failure and haematemesis are crude (Appendix 5C). Data on bladder cancer (squamous cell carcinoma) from *S. haematobium* infection are sufficient to suggest a causal relationship (Bedwani *et al.*, 1998, Kitinya *et al.*, 1986, Lucas, 1982, Mostafa *et al.*, 1999, Thomas *et al.*, 1990), but these data did not allow for estimating the prevalence, incidence or mortality rate. Estimates on incidence and mortality due to liver failure caused by *S. mansoni* infection were also not possible due to lack of data.

Results

Table 5.1 summarises the types of morbidity and pathology for which data were available, the method of measurement used in the different studies and the number of articles concerned.

Table 5.2 shows the estimated number of individuals with signs and symptoms due to infection with *S. haematobium* in sub-Saharan Africa. Haematuria (in the last 2 weeks) is predicted to occur in 70 (51–87) million individuals. Haematuria is generally thought to result from bladder pathology, therefore it is reassuring that our calculations predicted a comparable number of individuals with ultrasound detected minor bladder wall pathology, 88 (67–102) million. More serious pathology, major bladder wall pathology and moderate and major hydronephrosis was estimated to occur in respectively 18, 9.3 and 9.6 million individuals. In most West African countries the percentage of the total population with haematuria associated with *S. haematobium* infection is >15%, up to 24% in Gambia (Figure 5.1). Other countries with a high burden (percentage cases with haematuria of the total population) are Angola (18%), Malawi (20%), Mozambique (24%), Tanzania (18%) and Zimbabwe (16%). Kenya, Ghana, Mozambique, Tanzania and Nigeria are predicted to account for more than 50% of the morbidity cases associated with *S. haematobium*, partly due to their large populations. Other countries with many cases (>2 million haematuria cases) are Angola, Burkina Faso, Côte d'Ivoire and Sudan.

Table 5.1: Data used for the analysis: type of morbidity or pathology, method of measurement and number of articles identified. Details are reported in Van der Werf *et al.* (2002a) and Van der Werf *et al.* (submitted b) and Figure 5.3 (dysuria).

	Type of morbidity or pathology	Measured by	Number of articles
S. HAEMATOBIUM	Haematuria in last 2 weeks	Questionnaire	15
	Dysuria in last 2 weeks	Questionnaire	10
	Minor bladder pathology	Ultrasound	21
	Major bladder pathology	Ultrasound	8
	Moderate hydronephrosis	Ultrasound	17
	Major hydronephrosis	Ultrasound	13
S. MANSONI	Diarrhoea in last 2 weeks	Questionnaire	15
	Blood in stool in last 2 weeks	Questionnaire	21
	Abdominal pain	Questionnaire	22
	Hepatomegaly (MSL)	Clinical examination	30
	Splenomegaly	Clinical examination	43
	Ascitis	Clinical examination	9
	Haematemesis ever	Questionnaire	11

The estimated number of cases due to infection with *S. mansoni* is shown in Table 5.3. Hepatomegaly at MSL is predicted to occur in most individuals (8.5 million). Diarrhoea was estimated to occur in only 0.78 million individuals in sub-Saharan Africa, but this prediction was subject to a lot of uncertainty. In East African countries the percentage of the population affected by *S. mansoni* infection was generally higher than in West Africa (see Figure 5.2). More than 50% of the morbidity/pathology cases associated with *S. mansoni* infection can be found in Tanzania, DR Congo, Nigeria and Kenya. Sudan, Mozambique and Ethiopia also have a significant burden (>0.5 million hepatomegaly MSL cases).

Infection with *S. haematobium* does not seem to give widespread morbidity in Ethiopia, Uganda and Madagascar (prevalence ≤ 1%). Burundi, Rwanda, Equatorial Guinea and Eritrea are non or very low endemic for *S. haematobium*. Countries with low morbidity associated with *S. mansoni* infection are Rwanda, Gambia, South Africa and Mauritania. Whereas, Congo, Equatorial Guinea, Eritrea, Gabon, Guinea Bissau and Somalia are non or very low endemic for *S. mansoni*.

The number of cases with haematemesis (ever) was estimated at 0.9 million. From the assumed disease specific death rate and overall mortality (Appendix 5C), we estimated the annual incidence and mortality due to haematemesis for sub-Saharan Africa to be respectively 150,000 and 130,000. Using the association between prevalence of (heavy) infection with *S. haematobium* and prevalence of non-functioning kidney (Appendix 5C), we estimated 1.7 million individuals with at least one non-functioning kidney in sub-Saharan Africa. This corresponds with a predicted incidence of 180,000 and a mortality of 150,000 due to this cause per year.

Table 5.2. Estimated number of individuals with morbidity or pathology due to *S. haematobium* infection by age group in sub-Saharan Africa in millions (90% confidence interval). Intervals could be calculated for haematuria, dysuria and bladder pathology.

Category	Pre-school children	School children	Adults	Total
At risk of infection	71	168	196	436
Infected	14	56	43	112
Haematuria in last 2 weeks	9.5 (6.6 – 12)	33 (25 – 39)	28 (20 – 36)	70 (51 – 87)
Dysuria in last 2 weeks	3.6 (1.7 – 7.0)	17 (10 – 28)	11 (5.5 – 21)	32 (17 – 54)
Minor bladder wall pathology	12 (8.5 – 15)	41 (33 – 46)	35 (25 – 42)	88 (67 – 102)
Major bladder wall pathology	2.3 (0.5 – 3.5)	9.0 (3.0 – 13)	6.9 (1.6 – 10)	18 (5.1 – 27)
Moderate hydronephrosis	2.4	4.1	2.8	9.3
Major hydronephrosis	0	5.2	4.3	9.6

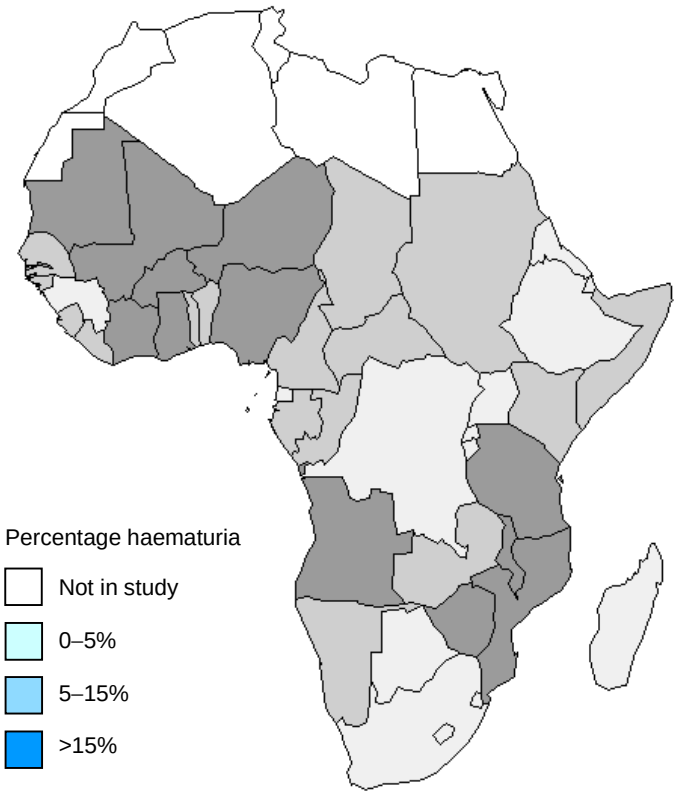

Figure 5.1: Map of Africa indicating predicted proportion of the total population with haematuria from *S. haematobium* infection by country.

Table 5.3. Estimated number of individuals with morbidity or pathology due to *S. mansoni* infection by age group in sub-Saharan Africa in millions (90% confidence interval). Intervals could be calculated for diarrhoea and blood in stool.

Category	Pre-school children	School children	Adults	Total
At risk of infection	65	152	177	393
Infected	4.7	25	23	54
Diarrhoea in last 2 weeks	0.034 (0.00 – 0.72)	0.42 (0.0 – 3.6)	0.32 (0.0 – 3.5)	0.78 (0.0 – 7.8)
Blood in stool in last 2 weeks	0.24 (0.16 – 0.69)	2.3 (1.6 – 4.1)	1.9 (1.3 – 3.7)	4.4 (3.0 – 8.3)
Hepatomegaly (MSL)	0.076	4.0	3.8	8.5
Splenomegaly	[0.61]	[2.9]	[2.8]	[6.3]
Ascitis	[0]	[0]	[0.29]	[0.29]
Haematemesis ever	[0]	[0]	[0.93]	[0.93]

[ ] use with caution, risk for confounding (splenomegaly) or estimations derived from limited literature data (ascitis and haematemesis)

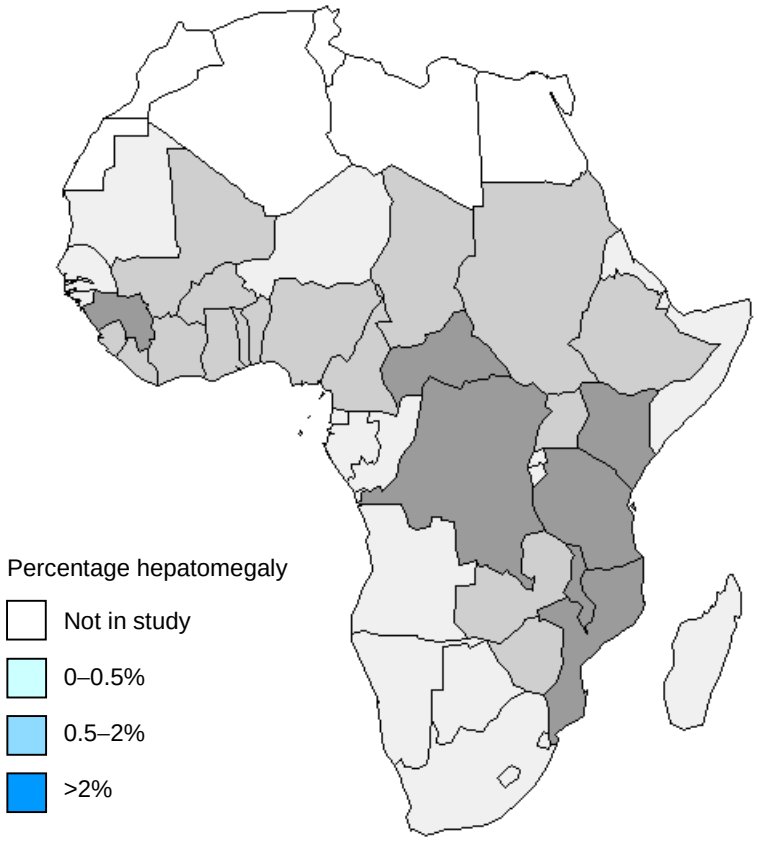

Figure 5.2: Map of Africa indicating predicted proportion of the total population with hepatomegaly (MSL) from *S. mansoni* infection by country.

Discussion

We attempted to estimate the numbers of individuals with morbidity or pathology due to schistosome infection by using all published data from field studies and taking into account 'confounding' factors. The quality of our estimates depends on the accuracy of the associations between prevalence of infection and morbidity, the quality of the available prevalence of infection data and the chosen degree of heterogeneity in prevalence of infection.

For some types of morbidity (major bladder wall pathology, haematemesis and ascitis) data were scarce resulting in predictions with wide uncertainty margins. The quality of the prevalence of infection and morbidity data differed among studies depending on the methods used and sample size. By aggregating all data we aimed to arrive at a grand average covering all endemicity levels and geographical areas. For most morbidity types and mortality, data were insufficient for estimating age-specific associations between prevalence of infection and prevalence of morbidity. Where data were available the association for children and adults appeared to be similar (Van der Werf *et al.*, 2002a). For several signs and symptoms related to schistosomiasis, data were insufficient for estimating an association between prevalence of infection and morbidity/pathology (*S. haematobium* and *S. mansoni*: cercarial dermatitis, pneumonia at invasion stage, anaemia, and ectopic lesions; *S. haematobium*: bladder cancer, genital lesions, and renal failure; *S. mansoni*: Katayama fever, liver failure and cor pulmonale). For more subtle consequences (reduction of growth, impaired cognitive development and reduced physical fitness) evidence was conflicting. Therefore, these morbidity types could not be included in the calculations. As a consequence, the burden caused by these signs and symptoms could not be included in the calculations of the total burden of schistosomiasis. Notably, this will result in an underestimation. The prevalence of infection data were derived from survey data (Brooker *et al.*, 2000b) and additional country information. These data also vary in quantity and quality.

The number of *S. haematobium* and *S. mansoni* infected individuals in sub-Saharan Africa used for the calculations was estimated to be 112 and 54 million respectively. It is difficult to compare these estimates with other estimates as some individuals may harbour both infections. Nevertheless, our values are comparable to those from other studies, e.g. 164 million schistosome infections in sub-Saharan Africa (Chitsulo *et al.*, 2000, Iarotski and Davis, 1981) and 200 million in the world (WHO, 1993).

As prevalences of infection data range between 0.0 and 1.0, a normal distribution of logit transformed data was used to account for heterogeneity. Our estimate of the general degree of heterogeneity (standard deviation, $\sigma = 0.6$) cannot be directly compared to the results of others (Chan *et al.*, 1994), as they did not use a logit transformation. However, the degree of heterogeneity from the non-transformed prevalence data in our study (σ^* ranging from 0.11 to 0.27) was comparable with that for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (σ^* ranging from 0.13 to 0.32, 0.12 to 0.37 and 0.12 to 0.35, respectively (Chan *et al.*, 1994)). We did not find a relationship between mean and standard

deviation as was found for Ascaris and Trichuris. To illustrate the importance of the degree of heterogeneity, we calculated the number of haematuria cases for different standard deviations. A $\sigma = 0.2$ results in 60 million haematuria cases, compared to 70 million for the chosen $\sigma = 0.6$. A higher standard deviation ($\sigma = 0.8$) predicted 75 million haematuria cases. Future work needs to focus on this heterogeneity and processes generating it. This will improve understanding of the spatial structure of schistosomiasis within endemic regions, and lead to a more precise mapping of distribution and more reliable estimates of disease burden.

We estimated that 6.4 million individuals have splenomegaly due to infection with *S. mansoni*. This figure should be used with much caution, as splenomegaly can also be the result of infection with *Plasmodium* species and these causes may concur as populations with a high prevalence of *S. mansoni* infection may have a high prevalence of malaria (mosquito breeding places in the irrigation canals where also the intermediate hosts of schistosomes could live) and, if so, effects of *S. mansoni* infection might be overestimated. Also, parasitic infections tend to cluster in poor populations (Booth *et al.*, 1998a).

Using our estimations, it can be inferred that for *S. haematobium* 63% of the infected individuals had haematuria in the last 2 weeks due to their infection, 28% dysuria and 8.5% major hydronephrosis. This agrees with the previously used simplistic assumption of 60% of the infected individuals being symptomatic and 10% having serious clinical morbidity (WHO, 1993). For *S. mansoni* the proportions with morbidity and/or pathology were much lower: 1.5% for diarrhoea, 8% for blood in stool and 16% for hepatomegaly (MSL). The association between *S. mansoni* prevalence and diarrhoea is not very distinct. This may account for our low estimate and wide 90% confidence interval. The real number of morbidity cases could be much higher. Others have reported on the varying relation between morbidity and prevalence of *S. mansoni* infection, i.e. areas with high prevalence of infection and low prevalence of morbidity and vice versa (Gryseels, 1989, Gryseels, 1992). The association between *S. haematobium* infection and morbidity seems to be more straightforward (Booth *et al.*, 1998b, Guyatt *et al.*, 1999a, Lengeler *et al.*, 1991, Lengeler *et al.*, 2000). It must be noted that our 90% confidence intervals ignore uncertainty in the original measurements of prevalences and uncertainty in prevalence of infection in countries is also not taken account of.

Our estimate of the number of deaths in sub-Saharan Africa attributed to schistosomiasis (150,000 by non-functioning kidney and 130,000 by haematemesis) is much higher than the estimate from the Global Burden of Disease Initiative (4000 deaths) (Murray and Lopez, 1996). The mortality estimates in this initiative have been based on models that use the relationship between general mortality and broad cause group mortality to estimate cause specific mortality in areas such as sub-Saharan Africa which do not have fully functioning vital registration systems. We believe that the new estimates presented in this paper will greatly facilitate the process of updating WHO figures for deaths due to schistosomiasis.

Our estimations have also to be treated with caution. The number of cases with haematemesis was derived from field studies, which could be biased due to the long recall period used in the questionnaires. Furthermore, haematemesis has a high mortality and individuals who died of exsanguination are not identified in a cross-sectional population study. Similarly, our estimate for non-functioning kidney is not very reliable. On the other hand, bladder cancer (*S. haematobium*) and liver failure (*S. mansoni*) will also be responsible for a certain number of deaths, but currently no data are available to provide even the weakest estimates. Few other studies described death due to schistosomiasis. Kheir *et al.* (1999) reported mortality due to schistosomiasis in a highly endemic village in Sudan (four individuals died from haematemesis in seven years (population size 1080)). And a study in Brazil reports a mortality rate due to schistosomiasis of 0.30/100,000. These studies did not allow for predicting a general mortality rate for *S. mansoni* infection.

Given the quality of the data available, we conclude that most of our morbidity estimates are at least a reasonable starting point to be used in (global) burden of disease calculations. Our study certainly provides the best attempt thus far to arrive at estimates using all information available. We have clearly demonstrated that number of cases with schistosomiasis-related signs and symptoms are high and easily concern millions. Moreover, we did not even include potentially important non-clinical morbidity, such as growth retardation. Our estimates of morbidity and pathology (and also death) associated with schistosomiasis underline that this classical tropical disease remains an important public health problem in sub-Saharan Africa. The global importance of schistosomiasis will further increase by including some endemic countries outside sub-Saharan Africa, such as Egypt (*S. haematobium* and *S. mansoni*), Brazil (*S. mansoni*) and China (*S. japonicum*).

Acknowledgements

The authors acknowledge the co-operation of H. Feldmeier, C.F. Hatz, J.R. Lambertucci, R. Olds, J. Richter. We thank J. Utzinger for providing data for the heterogeneity analysis. This study was performed within the WOTRO/NWO funded multidisciplinary programme 'Model-based decision support for schistosomiasis control in Ghana, Mali, Niger and Senegal' and was also funded by the department of Communicable Diseases Control, Prevention and Eradication, World Health Organization, Geneva, Switzerland and the Wellcome Trust (in the form of a Wellcome Trust Prize Fellowship to SB (No.062962).

APPENDIX 5A: Associating morbidity to infection

We related prevalence of morbidity (y-axis) to prevalence of infection (x-axis) on community level by using an expression related to the logistic regression curve (Van der Werf *et al.*, 2002a)

$$y = (a + bx^c)/(1 + bx^c) \quad (1)$$

This equation allows for baseline morbidity defined by parameter a (prevalence due to other diseases) and the degree of association is described by b and c. The derivative at $x = 0$ and $y = a$ equals zero, which means that no morbidity is due to schistosome infection at very low prevalences. It asymptotically (but not necessarily) reaches a prevalence of morbidity of 100%. To estimate the values of parameters a, b and c we used a Systat program (version 3.0, 1986) and fitted Equation 1 to all n data points. The fit was determined by assuming a binomial distribution for each data point i ($i = 1, \ldots, n$) and without assigning weight according to size of the population. As an example, Figure 5.3 shows the curve that was fitted for the association between prevalence of *S. haematobium* infection and dysuria. It shows a baseline prevalence of non-specific dysuria (i.e. dysuria due to other causes) of $a = 0.30$, and at around 0.25 prevalence of infection the prevalence of dysuria increases to 0.76.

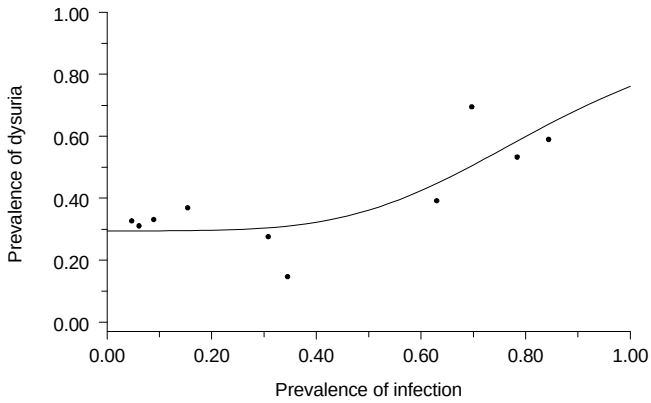

Figure 5.3: Association between prevalence of *S. haematobium* infection and prevalence of dysuria in last 2 weeks (measured by questionnaire). The association is described by Equation 1 with $a = 0.30$, $b = 1.94$ and $c = 4.23$. The data were derived from (Abdel-Wahab *et al.*, 1992a, Abdel-Wahab *et al.*, 2000b, Gabr *et al.*, 2000, Hammam *et al.*, 2000a, Hammam *et al.*, 2000b, King *et al.*, 1988a, Masaba *et al.*, 1983, Mungomba and Kalumba, 1995, Traquinho *et al.*, 1998, Warren *et al.*, 1979).

For hydronephrosis, hepatomegaly (MSL) and splenomegaly, fitting Equation 1 yielded biologically unrealistic curves (i.e. a sharp increase of pathology at low prevalence of

infection) due to sparse data. For these types of pathology we reduced the number of parameters by pre-setting the point of inflection at 1.0, hence $b = (c - 1)/(c + 1)$. Entering $b = (c - 1)/(c + 1)$ in Equation 1 results in

$$y = \frac{a + ((c-1)/(c+1))x^c}{1 + ((c-1)/(c+1))x^c} \qquad (2)$$

From the fitted expression, the curve with $a = 0$ (no baseline)

$$y = bx^c/(1 + bx^c), \qquad (3)$$

or its alternative with $b = (c - 1)/(c + 1)$, can be used to make predictions for a community on the morbidity potentially due to infection with schistosomes. For further details see Van der Werf (2002a).

Data sources, graphical plots, data points and parameters b and c of the equations that are used for predicting the prevalence of morbidity in a community are described Van der Werf (2002a), (Van der Werf *et al.*, submitted b) and in the report *Morbidity and infection with schistosomes or soil-transmitted helminths* by Marieke J. van der Werf and Sake J. de Vlas (at the request of WHO/PVC/CPE). Parameters for morbidity and pathology due to infection with *S. haematobium* are $b = 1.04$, $c = 1.41$ for haematuria, $b = 1.94$, $c = 4.23$ for dysuria, $b = 2.45$, $c = 1.66$ for minor bladder pathology, $b = 0.26$, $c = 1.75$ for major bladder pathology, $b = 0.27$, $c = 1.74$ for moderate and major hydronephrosis and $b = 0.11$, $c = 1.23$ for major hydronephrosis. For predicting morbidity due to *S. mansoni* infection, the parameters of the equation are $b = 0.27$, $c = 7.70$ for diarrhoea, $b = 0.69$, $c = 4.95$ for blood in stool, $b = 0.22$, $c = 1.56$ for hepatomegaly (MSL), $b = 0.12$, $c = 1.27$ for splenomegaly, $b = 0.029$, $c = 3.83$ for ascitis and $b = 0.024$, $c = 1.63$ for haematemesis. The association between *S. mansoni* infection and abdominal pain was non-conclusive. For haematemesis and ascitis we assumed all morbidity cases to be in the adult group and the reported prevalence of infection to reflect the total population.

APPENDIX 5B: Estimating the prevalence of morbidity in a country

The equations described in Appendix 5A allow for the estimation of morbidity in individual communities (mostly villages) but cannot be used to predict prevalences of morbidity on an aggregated (e.g. country) level. Most morbidity will occur in villages with the highest prevalence of infection. However, even countries with a low mean prevalence will have some villages with relatively high prevalences of infection. Therefore, morbidity would be underestimated if the mean country prevalence of infection were used for the calculation. This is due to convexity of the relationship between community prevalence of infection and morbidity. Thus, we have to take into account the distribution of prevalences of infection in a country (Chan *et al.*, 1994). Subsequently using Equation 3, the prevalence of morbidity y in a country with mean prevalence of infection μ is predicted by

$$y = \int_0^1 \frac{bx^c}{1 + bx^c} \Pr(x \mid \mu) \qquad (4)$$

where $\Pr(x \mid \mu)$ denotes the probability of a community having prevalence of infection x given a country with mean μ.

The distribution of prevalences within a country, can be gleaned from two data sets for *S. haematobium* (kindly provided by (Guyatt *et al.*, 1999a) and (Lengeler *et al.*, 1991)) and four data sets for *S. mansoni* (kindly provided by (Barakat *et al.*, 1995, Gryseels and Nkulikyinka, 1988, Lengeler *et al.*, 2000) and (Utzinger *et al.*, 2000). To allow for prevalences varying between at least 0.0 and at most 1.0, we have fitted a normal distribution to the logit transformed ${}^{10}\log(P_i / (1 - P_i))$ prevalences P_i (i = 1, .., N) and estimated the standard deviation σ for each data set.

Figure 5.4 shows an adequate fit for all data sets, but the standard deviations of the distributions ranged from σ = 0.20 to 0.87. Most data concerned prevalences in a district. Therefore, we assumed that the standard deviation for a country will be relatively high but not necessarily equal to the district with the largest heterogeneity. For both *S. haematobium* and *S. mansoni*, we chose a standard deviation of σ = 0.6 (comparable with Côte d'Ivoire) for country/region prevalence of infection to calculate the mean prevalence of morbidity in a country.

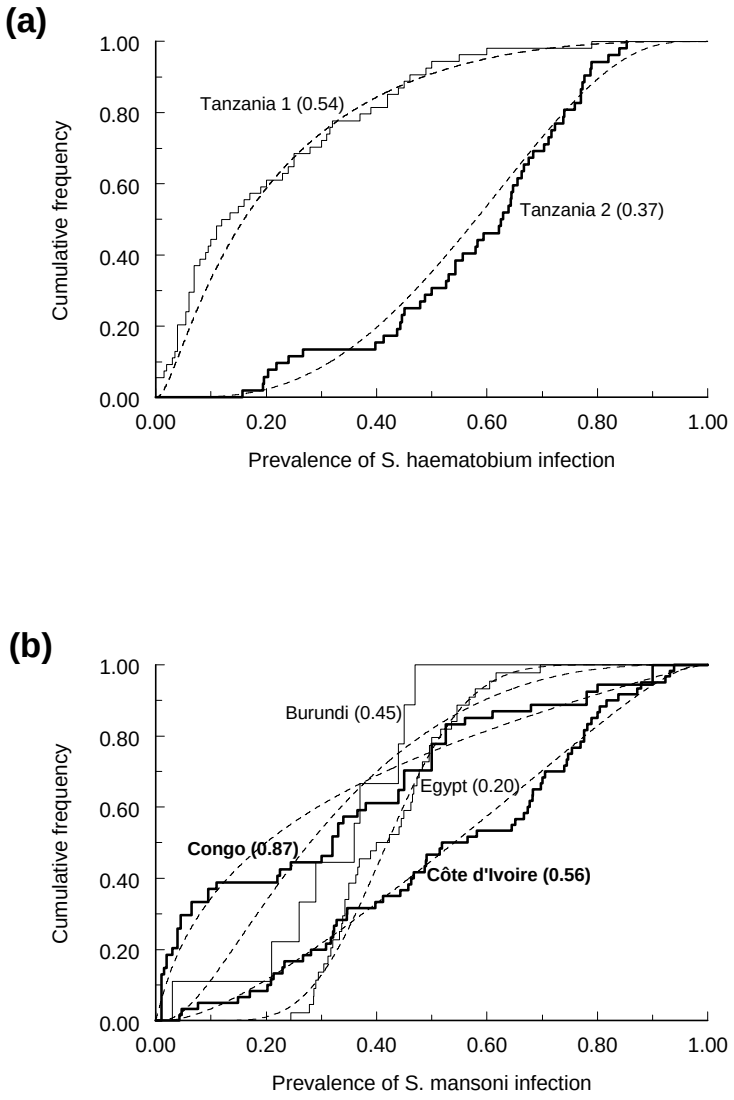

Figure 5.4: Cumulative distribution of (a) *S. haematobium* prevalences in Kilombero district of Morogoro Region, Tanzania [Tanzania 1], *N* (number of schools or communities) = 54, mean = 0.16 ('anti-logit' of the mean of logit transformed data) and σ = 0.54 (Lengeler *et al.*, 1991) and Magu district of Mwanza Region, Tanzania [Tanzania 2], *N* =52, mean = 0.58 and σ = 0.37 (Guyatt *et al.*, 1999a). And, (b) *S. mansoni* prevalences, of the Rusizi Plain, Burundi, *N* = 9, mean = 0.28 and σ = 0.45 (Gryseels and Nkulikyinka, 1988), the region of Kafr El Sheikh governorate, Egypt, *N* = 44, mean = 0.42 and σ = 0.20 (Barakat *et al.*, 1995), and (c) the town of Matadi and the administrative zone of Songololo, Congo, *N* = 54, mean = 0.20 and σ = 0.87 (Lengeler *et al.*, 2000), and the region of Man, western Côte d'Ivoire, *N* = 60, mean = 0.54 and σ = 0.56 (Utzinger *et al.*, 2000) (data were kindly provided by the authors). The value between brackets is standard deviation σ of logit transformed prevalences. The steeper the line around 50% cumulative frequency, the lower the value of σ. The dashed lines represent the fitted distributions.

APPENDIX 5C: Estimating mortality due to non-functioning kidney and haematemesis

Incidence of mortality was estimated from the (estimated) number of cases with life-threatening morbidity, here non-functioning kidney due to *S. haematobium* and haematemesis due to *S. mansoni*. By assuming an exponential distribution, the disease specific annual death rate u can be obtained from follow-up studies by

$$u = -\ln(1-p)/t \qquad (5)$$

in which p is the proportion dead within a period t in years. Given a number of cases with morbidity c, and assuming no time-trends, the incidence i is approximated by

$$i = c\,(m+u) \qquad (6)$$

in which m is the general mortality rate in the population. The number of disease specific deaths d per year can be calculated from

$$d = i * u/(m+u) = c\,u \qquad (7)$$

To the best of our knowledge, only one published study provided data to infer a death rate of individuals with non-functioning kidney and only two studies for haematemesis. Out of seven individuals with non-functioning kidney, three died within 6 year (Forsyth *et al.*, 1970), leading to $u = 0.09$ per year for non-functioning kidney (Equation 5). For haematemisis, 5 out of 25 patients died within 1 year (Kiire, 1989) and 4 out of 27 died within 28 months (Richter *et al.*, 1998). This associates with an average of $u = 0.14$ per year. The general mortality rate ($m = 0.02$/year) was obtained from http://www.statistical-data.org/index.html (16 August 2001).

The number of cases with haematemesis (ever) at cross-section could be obtained from our estimates using the prevalence of infection (see Appendix 5A). For non-functioning kidney (detected by intravenous pyelogram), only two studies were available to arrive at an association between infection and morbidity (Forsyth, 1969, Forsyth and Bradley, 1966). As this was not sufficient to fit equation 1 or 2, we chose a different procedure. First, we assumed that non-functioning kidney shows a linear association with the number of individuals with heavy infections (> 50 eggs per 10 ml); an estimate of this number for a given community prevalence of infection was obtained from an existing egg count model (De Vlas *et al.*, 1992). Second, we assumed that all non-functioning kidney cases in *S. haematobium* endemic areas are caused by the infection. Forsyth and Bradley (1966)

investigated 794 *S. haematobium* infected individuals in a population with prevalence 65% (i.e. about 405 individuals > 50 eggs per 10 ml) by intravenous pyelogram and detected 36 with at least one non-functioning kidney. Forsyth (1969) found among 751 infected individuals in a population with prevalence 42% (i.e. about 120 individuals > 50 eggs/10 ml), five cases with at least one non-functioning kidney. This means that on average 0.064 × the prevalence of individuals with heavy infection in a community will have at least one non-functioning kidney.

Part II

Schistosomiasis case management in West Africa

6

Schistosomiasis control in Ghana: case management and means for diagnosis and treatment within the health system

Van der Werf, M. J., Bosompem, K. M. and De Vlas, S. J. Schistosomiasis control in Ghana: case management and means for diagnosis and treatment within the health system. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, in press

Abstract

An essential component of integrated schistosomiasis control as promoted by WHO is adequate clinical care for patients presenting at health care facilities. We evaluated functioning of the Ghanaian health system for diagnosis and treatment of schistosomiasis by interviewing health workers from 70 health care facilities in four geographical areas.

Results from presentation of 4 hypothetical cases and a subsequent interview demonstrated that patients presenting with symptoms related to schistosomiasis have a small chance of receiving adequate treatment: often health workers do not recognise the symptoms, especially those of *S. mansoni*; patients are frequently referred for a diagnostic test or treatment with a large risk of non-compliance; and praziquantel was not available in 78% of the health care facilities with reported schistosomiasis in their coverage area. The overall cost of treatment is considerable: 2.13 Euro for *S. haematobium* and 1.81 Euro for *S. mansoni* patients, with the drug taking approximately 40% of the total cost.

To better meet WHO recommendations for passive case detection as part of integrated schistosomiasis control, the Ghanaian health system needs to emphasise training of health workers in schistosomiasis case recognition and case management and increase the availability of praziquantel. Experiences from other West-African countries indicate that this is feasible.

Introduction

In Ghana, foci endemic for *Schistosoma haematobium* and/or *S. mansoni* infection are known for several decades (McCullough, 1957, McCullough and Ali, 1965, Edington, 1957, Onori *et al.*, 1963). Since the completion of the Akosombo dam across the Volta River in 1964, urinary schistosomiasis prevalence in Ghana has increased steadily along the shores of the man-made Volta lake and the Volta River (Scott *et al.*, 1982, Wen and Chu, 1984, Klumpp and Webbe, 1987). Also, in other parts of the country, construction of dams and irrigation facilities have promoted the spread of schistosomiasis (*S. haematobium* and *S. mansoni*) (Zijlmans *et al.*, 1989, Amankwa *et al.*, 1994). The Volta River Authority has started a schistosomiasis control programme that initially used molluscicide to kill the intermediate snail hosts and control the infection. After the drug praziquantel became available, the team started to visit affected villages to deliver mass treatment. In other parts of the country no official control programmes exist, so control of schistosomiasis is confined to treatment of clinical cases by local health workers.

Since 1991, the main principle of schistosomiasis control recommended by the World Health Organization (WHO) is morbidity control through measures implemented in the primary health system (WHO, 1993). It was recognised that the first essential component of integrated control should be adequate clinical care for patients presenting at the health care facilities (passive case detection) (Engels *et al.*, 2002). This requires adequate knowledge of the health workers about the symptoms of the infection, availability of diagnostic and therapeutic means, and adequate prescription of treatment (praziquantel).

By interviewing medical staff of 70 health care facilities in Ghana, we determined the clinical care that patients can expect when they present with schistosomiasis symptoms. In particular, we compared the functioning of the Ghanaian health system for the control of schistosomiasis with the three main recommendations of WHO for passive case detection (WHO, 1993): (1) if a laboratory is available, sensitive diagnostic tests (e.g. urine filtration or centrifugation for *S. haematobium* and Kato Katz for *S. mansoni*) should be used for diagnosis; (2) if diagnostic facilities are not available in the health care facility, case detection should be performed on presenting symptoms (symptom-based treatment); and (3) symptomatic cases should be treated with praziquantel at all levels of the health system.

Methods

Ghanaian health system

The health services in Ghana are organised according to the primary health care principle (WHO, 1978). The first level of contact with patients is in the health centres. These are staffed with medical assistants or nurses helped by other personnel such as ward assistants. Their main task is providing basic primary care to the population in their area. This includes patients presenting with symptoms of early schistosomiasis infection, such as haematuria and blood in stool. Cases that can not be handled at health centre level are

referred to the district hospital, which is under the direction of a medical doctor. These hospitals are equipped to give all curative and preventive services at primary care level. Complicated cases (including patients with long-term consequences of schistosomiasis, such as kidney failure and haematemesis) are referred to the regional hospitals. Most districts also have private clinics, mission clinics and/or mission hospitals. Normally, laboratory diagnosis can be performed at district, regional and mission hospitals. Mission clinics and hospitals are part of the Christian Health Association of Ghana (CHAG). Patients can buy drugs at the health system but also from private pharmacies and from drug peddlers (persons who travel from place to place to sell drugs).

The Ghanaian Ministry of Health introduced the 'Cash and Carry' system in 1992 (based on Bamako initiative) (Biritwum, 1994). This requires that patients pay for registration, diagnostic tests and drugs. To improve financial access, paupers are exempted from payment, but in reality this involves only a small part of the population. Other exemptions are patients with tuberculosis and leprosy, psychiatric patients, pregnant women and children under 4 years (Nyonator and Kutzin, 1999).

Study area and health care facilities

The study was performed in April and May 2000, in Ghana. Four geographical areas were selected and in each area two or three representative districts were chosen. The surveyed districts were Kassena-Nankana, Builsa and West Mamprusi (North Ghana), North Tongu and South Tongu (East), Bosomtwi Kwanwoma and Atwima (Centre) and Kraboa Coaltar (South) (Figure 6.1).

In each district, the district hospital, one mission hospital (if present) and a random sample of health centres and mission clinics were selected. If private clinics were present in a district, one was selected. In total, we selected 10 health care facilities per district, or all health care facilities if there were eleven or less present.

Interviews and data collection

For the interview we used an adapted version of a successfully applied questionnaire (translated into English) developed for a comparable study in Senegal (Van der Werf *et al.*, 2002b). Each selected health care facility was visited and the person in charge interviewed. If this person was not present, the second in command was interviewed. We did not reveal the specific aim of our study: evaluation of schistosomiasis control as performed by the health system. After introduction, we presented four hypothetical cases with symptoms related to *S. haematobium* and *S. mansoni* infection in random order: (A) 10 year old girl with blood in urine; (B) 40 year old man with blood in urine and painful urination; (C) 10 year old boy with abdominal discomfort and bloody diarrhoea and (D) 30 year old woman with diarrhoea and abdominal discomfort. The respondents were requested to imagine that these cases visited their health care facility and to explain their usual case management policy for such patients. Thereafter, we revealed the focus of our study and continued by asking the respondents to list symptoms caused by *S. haematobium* or *S. mansoni* infection.

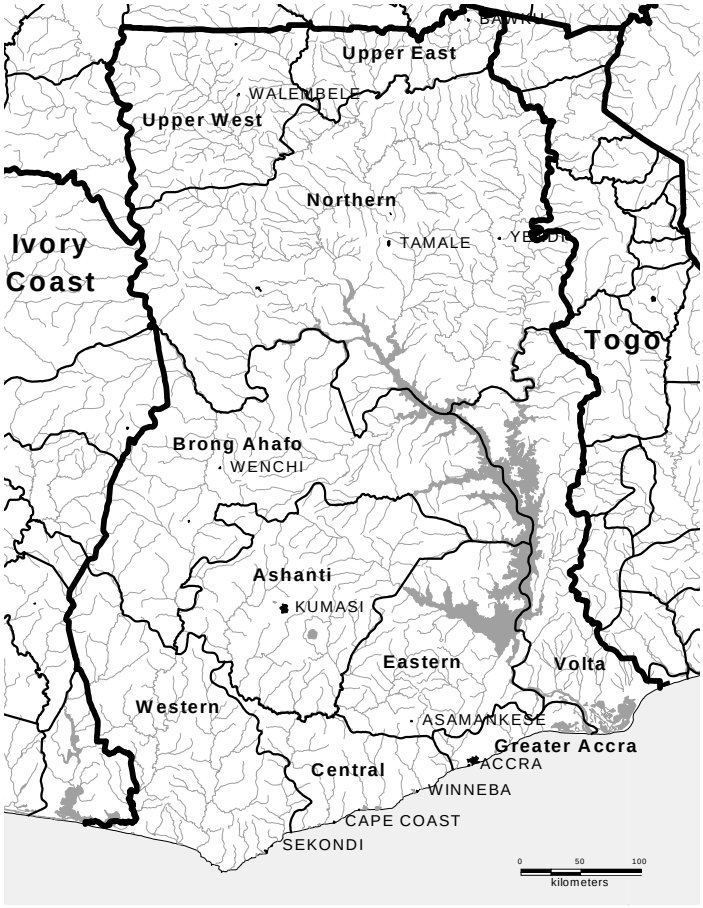

Figure 6.1: Map of study area in Ghana.

Then we asked if these infections were present in their coverage area. Respondents working in areas with reported schistosomiasis endemicity were asked further questions about their practises for patients presenting with symptoms caused by haematuria (*S. haematobium* infection) and blood in stool/bloody diarrhoea (*S. mansoni* infection).

We concluded the interview by collecting information about the size of the population covered and number of curative consultations and schistosomiasis patients in 1999. We recorded the availability of diagnostic materials and the number of praziquantel tablets in stock at the time of the interview. Finally, the price of registration, diagnostic test, praziquantel and public transport to the nearest referral centre was recorded. For all questions we tried to obtain the exact value, otherwise an estimated value was asked for. Sometimes, information was provided by mail or telephone up to a few days after the interview.

If the respondent did not know schistosomiasis or if it was unknown whether schistosomiasis was present in the coverage area, the data were analysed as not having schistosomiasis in the coverage area. The replies given by different professional groups or primary health care levels were statistically compared using the Chi-square/Fisher's exact test (SPSS). A p-value < 0.05 was considered significant.

Cost analysis

Calculation of the average costs of treatment is described by Van der Werf *et al.* (2002b). Briefly, costs of treatment for schistosomiasis were calculated by adding the price of registration, diagnostic test and treatment with four praziquantel tablets (dose for an adult). If the health worker reports to refer patients for a diagnostic test or for buying praziquantel, we used the price of a diagnostic test and/or praziquantel in the referral centre. If health workers referred to a health care facility outside the study sample or private clinic/pharmacy, we used the mean costs of a diagnostic test or praziquantel in hospitals. If a diagnostic test is not requested costs are nil. Also, if patients are not referred for diagnostic test or treatment transportation costs are nil. All costs are presented in Euros. In May/June 1999, 1 Euro was approximately 4000 cedis (local currency).

Results

A total of 70 health care facilities were surveyed (Table 6.1). Forty-nine respondents (70%) reported presence of *S. haematobium* in their coverage area, 12 (17%) also reported *S. mansoni* infection. In our study there were no areas with only reported *S. mansoni*. Twenty-one percent (21%) of the health workers could not recall about the existence of *S. mansoni*. Two others (2.9%) did not know whether *S. mansoni* infection existed in their coverage area, whilst one respondent (1.4%) did not know about the presence of *S. haematobium* infection in the coverage area of the health care facility.

Table 6.1: Characteristics of the 70 visited health care facilities (HCF) surveyed in Ghana.

Health care facility	No.	Population covered by HCF in thousands, median (range)*	No. of consultations 1999 in thousands, median (range)**	No. of HCF reporting presence of schistosomiasis in its coverage area (%)	
				S. haematobium	*S. mansoni*
District hospital	9	110 (54–234)	16.4 (1.8–35)	8 (89)	3 (33)
Mission hospital	3	163 (128–200)	49 (18–63)	3 (100)	3 (100)
Health centre	45	15 (0.8–69)	2.2 (0.2–28)	26 (58)	4 (9)
Mission clinic	8	13 (7.9–26)	1.4 (0.6–32)	7 (88)	1 (13)
Private clinic	5	43 (8.0–156)	3.6 (1.0–25)	5 (100)	1 (20)
Total	70			49 (70)	12 (17)

* Population figures of one mission hospital and one health centre were not available and two private clinics did not indicate a specified population.

** Four health centres and 1 mission clinic did not practice the whole year of 1999 and were therefore not included in 'Number of consultations in 1999'.

Most hospitals employed at least one medical doctor and/or medical assistant (Table 6.2). Health centres and mission clinics were mainly staffed by nurses. The beds in health centres and private clinics were only used for short-term observation. Laboratories were in possession of all necessary equipment for performing urine centrifugation (microscope, tubes, glass-slides and centrifuge) and direct smear tests (microscope and glass-slides). The Kato-Katz test was not used for the diagnosis of *S. mansoni* in the visited health care facilities and the necessary materials were not available. Only 11 health care facilities of 49 with reported schistosomiasis in the coverage area had praziquantel available at the time of the interview. The remainder referred to another health care facility or private pharmacy. However, out of 5 private pharmacies in schistosomiasis endemic areas visited during the survey, none had praziquantel available (not in table).

Table 6.2: Availability of personnel and equipment in 49 Ghanaian health care facilities with reported schistosomiasis in their coverage area.

Personnel/equipment	No. of health care facilities with different personnel and equipment		
	Hospital (n=11)	Health centre and mission clinic (n=33)	Private clinic (n=5)
Doctors, median (range)	1 (0–6)	0 (0–1)	0 (0–1)
Medical assistants, median (range)	1 (0–2)	0 (0–2)	0 (0–2)
Nurses, median (range)	16 (8–67)	4 (1–11)	1 (1–3)
Beds, median (range)	54 (8–220)	4 (0–21)	2 (0–10)
Laboratory	10 (91%)	1 (3%)*	2 (40%)
Praziquantel	6 (55%)	4 (12%)	1 (20%)

* Two health centres did have a laboratory, but the laboratory was not functioning because of absence of the laboratory technician

Urinary schistosomiasis was mentioned as initial diagnosis for hypothetical cases A and B by the majority of the respondents in areas reported to be endemic for *S. haematobium* (Table 6.3). In contrast, cases C and D were hardly ever given the initial diagnosis of (intestinal) schistosomiasis. If the 4 cases would really concern schistosomiasis patients, we can conclude that the ultimate probability of prescription of praziquantel without referral was only 43%, 37%, 58% and 67%, respectively. For cases C and D, praziquantel was only prescribed after a positive diagnostic test, for A and B, one-third would receive praziquantel treatment directly.

Ninety-six percent of the health care workers reported haematuria, the main presenting symptom of *S. haematobium* infection, when asked to mention symptoms related to *S. haematobium* infection (Figure 6.2a). Symptoms less commonly or not associated to infection with *S. haematobium* were also mentioned (e.g. fever, loss of appetite). There was no significant difference in (the quality of) the answers given by doctors and other health workers. There was also no difference in answers given by health workers from areas with reported *S. haematobium* and areas without reported *S. haematobium*. Eighty percent of the

Table 6.3: Diagnosis and treatment strategy for 4 hypothetical cases in health care facilities with reported *S. haematobium* or *S. mansoni* in their coverage area.

Diagnosis and action	*S. haematobium* (n=49)		*S. mansoni* (n=12)	
	Case A* (%)	Case B* (%)	Case C* (%)	Case D* (%)
Initial diagnosis schistosomiasis	45 (92)	31 (63)	2 (17)	0 (0)
Action				
Direct prescription of praziquantel	8 (16)	5 (10)	0 (0)	0 (0)
Prescription of praziquantel if schistosome eggs found in diagnostic test#	13 (27)	13 (27)	7 (58)	8 (67)
Prescription of other drug&	8 (16)	14 (28)	5 (42)	4 (33)
Referred for diagnosis and/or treatment	20 (41)	17 (35)	0 (0)	0 (0)

* Hypothetical cases were: 10 year old girl with blood in urine (Case A); 40 year old man with blood in urine and painful urination (Case B); 10 year old boy with abdominal discomfort and bloody diarrhoea (Case C); and 30 year old woman with diarrhoea and abdominal discomfort (Case D).

Diagnostic test for *S. haematobium* is urine centrifugation test and diagnostic test for *S. mansoni* is direct smear test

& Mainly antibiotics, metrifonate, metronidazole and ORS

respondents working in endemic areas requested a diagnostic test to confirm the symptomatic diagnosis for patients suspected of *S. haematobium* infection that presented with haematuria (Table 6.4). Fourteen (29%) health workers prescribed the treatment recommended by WHO (40 mg praziquantel per kilogram bodyweight), 12 (24%) prescribed other dosages of praziquantel (1 health worker prescribed 30 mg per kilogram bodyweight, 3 prescribed 60 mg per kilogram bodyweight and 8 did not prescribe per kilogram bodyweight), 2 (4%) prescribed metrifonate and 4 (8%) prescribed other drugs for treatment of *S. haematobium* (antibiotics or metronidazole). Of the 9 (18%) health workers who performed symptom-based treatment, 6 (67%) prescribed praziquantel and 4 (67%) of them had it in stock at the time of interview.

The main presenting symptom of early *S. mansoni* infection, bloody diarrhoea or blood in stool, was mentioned by 41% of the respondents (Figure 6.2b). Symptoms occurring in the advanced stage of the infection such as ascites and haematemesis were not mentioned at all. Often, symptoms less commonly associated with *S. mansoni* infection were mentioned (i.e. itching, fever and nausea). The symptoms blood in stool and abdominal discomfort were more frequently mentioned by doctors compared to other health workers (p-value respectively 0.013 and 0.001). All doctors could mention at least one symptom related to *S. mansoni* infection, whereas of the other health care workers 25% did not know *S. mansoni* and 30% could not mention a symptom. Health workers that reported *S. mansoni* infection in their coverage area more often reported the symptoms blood in stool, abdominal discomfort and diarrhoea (p-value respectively 0.002, 0.050 and 0.014) compared to health workers that reported no *S. mansoni* in their coverage area. For patients suspected of *S. mansoni* infection and reporting with blood in stool/bloody diarrhoea, 67% of the respondents from areas with reported *S. mansoni* infection would request a diagnostic test to confirm the symptomatic diagnosis (Table 6.4). Seven (58%) health care facilities with

Table 6.4: Management of patients suspected of schistosomiasis and reporting with haematuria or blood in stool/bloody diarrhoea in Ghanaian health care facilities in areas where respectively *S. haematobium* (n = 49) or *S. mansoni* (n = 12) is reported to be present.

Case management and treatment	No. of health care facilities performing different case management (%)		
	Hospital	Health centre & mission clinic	Private clinic
Haematuria (for S. haematobium)			
Symptom not mentioned	0 (0)	1 (3)	0 (0)
Symptom-based treatment with praziquantel	0 (0)	6 (18)	0 (0)
Symptom-based treatment with other drug*	0 (0)	2 (6)	1 (20)
Diagnosis by urine centrifugation, if positive** praziquantel	10 (91)	1 (3)	1 (20)
Diagnosis by urine centrifugation, if positive** other drug#	0 (0)	0 (0)	2 (40)
Referral for diagnostic test, if positive** praziquantel	0 (0)	7 (21)	1 (20)
Referral for diagnostic test and treatment	1 (9)	16 (48)	0 (0)
Total	11 (100)	33 (100)	5 (100)
Blood in stool and bloody diarrhoea (for S. mansoni)			
Symptom not mentioned	2 (33)	0 (0)	0 (0)
Symptom-based treatment with praziquantel	0 (0)	1 (20)	1 (100)
Diagnosis by direct smear, if positive** praziquantel	4 (67)	1 (20)	0 (0)
Referral for diagnostic test, if positive** praziquantel	0 (0)	2 (40)	0 (0)
Referral for diagnostic test and treatment	0 (0)	1 (20)	0 (0)
Total	6 (100)	5 (100)	1 (100)

* antibiotics, metronidazole and metrifonate

** positive for diagnosis means *S. haematobium* eggs detected in urine sample or *S. mansoni* eggs detected in stool sample

metrifonate and antibiotics

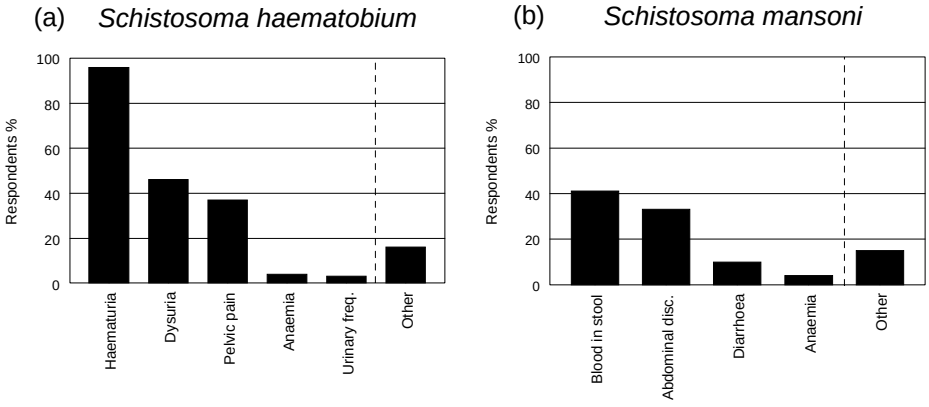

Figure 6.2: Symptoms mentioned by respondents (n=70) to be related to *S. haematobium* (a) and *S. mansoni* (b) infection. Respondents were requested to mention as many symptoms related to schistosomiasis as possible. Fifteen health workers did not know *S. mansoni* infection and 18 could not mention a symptom caused by *S. mansoni* infection. Urinary freq. is urinary frequency. Abdominal disc. is abdominal discomfort. "Other" refers to symptoms less commonly associated with schistosomiasis. In order of importance, these were fever, problems with urinating, sexual weakness, female infertility, loss of weight and loss of appetite for *S. haematobium*, and mucous in stool, fever, nausea, vomiting, colic, losing weight, itching, itching in anal region, constipation, haematuria, dark stool, waist pain, bloated abdomen, looking weak and loss of appetite for *S. mansoni.*

reported *S. mansoni* in the area prescribed the recommended treatment. One (8%) health worker prescribed praziquantel at 30 mg per kilogram bodyweight, and 3 (25%) prescribed 60 mg per kilogram bodyweight and one (8%) referred to another health care facility for treatment. Symptom-based treatment for patients presenting with the main symptom of *S. mansoni* infection was performed in 2 (18%) health care facilities. One of the two, a private clinic, really had praziquantel in stock.

Registration costs were higher in hospitals and private clinics compared to health centres and mission clinics (Anova, p = 0.019), Table 6.5.

Table 6.5: Mean costs of registration, diagnostic test and treatment in different types of health care facilities in Euro.

Itemized services	Cost in different health care facilities			
	Hospital	Health centre and mission clinic	Private clinic	All
S. haematobium reported in area[*]	11	30	2	43
Registration	0.49	0.29	0.75	0.36
Urine centrifugation	0.48	0.32	0.36	0.37[#]
4 praziquantel tablets	0.87	0.78	1.05	0.82
Transportation to other HCF	0.18	0.76	0.20	0.59[&]
Total costs	2.02	2.16	2.37	2.13
S. mansoni reported in area	6	5	1	11
Registration	0.47	0.27	0.50	0.39
Direct smear	0.42	0.20	0.00	0.29[#]
4 praziquantel tablets	0.73	0.89	1.20	0.84
Transportation to other HCF	0.05	0.65	0.00	0.30[&]
Total costs	1.67	2.01	1.70	1.81

[*] 1 health centre, 2 mission clinics and 3 private clinics did not prescribe praziquantel for treatment of *S. haematobium* and were excluded for the calculation

[#] If a diagnostic test was not requested its cost was nil. The average costs of a diagnostic test in health care facilities where test is requested is 0.40 Euro for *S. haematobium* and 0.35 Euro for *S. mansoni*

[&] If a patient is not referred the transportation costs are nil. The average transportation cost for patients that are referred are 0.80 Euro for *S. haematobium* patients and 0.89 Euro for *S. mansoni* patients

Mean price for a urine centrifugation test is 0.37 Euro (range 0.08–0.75). Patients visiting health centres or mission clinics paid less for a diagnostic test compared to patients visiting hospitals or private clinics (Anova, p=0.043). For diagnosis of *S. mansoni* infection by direct smear test the mean price is 0.29 (range 0.13–0.63). Prices for diagnostic tests in the different types of health care facilities were similar. As most health workers referred their patients to a hospital or private pharmacy for treatment, comparison between prices for treatment in different health care facilities was not possible. Costs of additional transportation are substantial for patients visiting health centres and mission clinics because these facilities frequently refer patients for diagnostic tests and/or treatment. The total costs for treatment of *S. haematobium* or *S. mansoni* infection was comparable between hospitals, health centres and mission clinics, and private clinics with treatment taking about 40% of overall costs.

Discussion

To meet WHO recommendations for integrated schistosomiasis control would require several alterations within the Ghanaian health system. In clinics and hospitals with diagnostic facilities, WHO recommends case detection by sensitive diagnostic tests (WHO-recommendation 1). In our sample, only 13 (27%) health care facilities had a laboratory available and were capable of performing a laboratory test to diagnose *S. haematobium* or *S. mansoni* infection. These laboratories all used the urine centrifugation test for diagnosing *S. haematobium* infection and the direct faecal smear test for *S. mansoni*. The use of this simple but insensitive diagnostic technique for *S. mansoni* will certainly leave some patients undiagnosed.

In health care facilities without diagnostic facilities the identification of patients should preferably be symptom-based (WHO-recommendation 2). One essential requirement for adequate case detection is knowledge of the main presenting symptoms of schistosomiasis, which was sufficient for *S. haematobium* but limited for *S. mansoni* (41% mentioned blood in stool). Hypothetical cases C and D confirmed that patients with symptoms related to intestinal schistosomiasis have little chance of being identified as such. Both blood in stool and abdominal pain were frequently interpreted as coming from amoebiasis, food poisoning or bacterial or parasitic intestinal infection. Therefore, we conclude that passive case detection for *S. mansoni* requires a more specific clinical algorithm to distinguish between schistosomiasis patients and other diseases. In case of no diagnostic facilities, most clinics referred their patients to another health care facility for a test. This results in extra costs for the patient and a high risk of non-compliance.

In our sample, most health workers reported to prescribe praziquantel to patients identified by symptoms or diagnostic test (WHO-recommendation 3). As only 11 out of 49 health care facilities had the drug in stock at the time of the interview most had to refer their patients to another health care facility or private pharmacy for buying drugs, again entailing a risk of non-compliance. We realise that the reported actions might not fully correspond with real actions (Russell *et al.*, 1991, Kopelow *et al.*, 1992). However, it is encouraging that the results about case management from the questionnaire and the hypothetical cases are comparable.

Health workers that reported not to have schistosomiasis in their coverage area were not questioned about their management of patients presenting with symptoms of schistosome infection because it was considered likely that they would never suspect a patient of schistosomiasis and therefore never prescribe adequate treatment. Data from laboratories in the visited regions suggest that *S. haematobium* is endemic in Kraboa Coaltar district in Eastern Region and Bosomtwi Kwanwoma district in Ashanti region and both *S. haematobium* and *S. mansoni* are endemic in the other visited districts. There are indications that especially the presence of *S. mansoni* infection is not known by many health workers (A. Danso-Appiah, personal communication). Therefore, a number of health workers not questioned about their management of schistosome patients may have schistosome

patients presenting at their health care facility, but they will most likely never receive adequate treatment.

The largest part of the cost for treatment of schistosomiasis is due to praziquantel and extra transportation after referral. Introduction of symptom-based treatment or wider availability of praziquantel will reduce the costs for transportation. A reduction in the price of praziquantel will also help to increase the financial accessibility of treatment. In Ghana, the Gross National Product per capita in 1999 was USD 390 (one USD equalled 1 Euro in May 2000) (http://devdata.worldbank.org/external, 17-04-2001). For families who live in relatively poor rural areas where schistosomiasis is endemic, it may not be feasible to spend approximately 2.00 Euro for treatment of schistosomiasis, especially because other (more serious) diseases such as malaria will also require medical expenditure.

In conclusion, many patients with symptoms of (early) schistosome infection that visit health care facilities in Ghana will not be identified as such, especially when having symptoms related to *S. mansoni* infection. Most health workers request a diagnostic test (often with limited sensitivity), which does not conform to WHO recommendations for integrated schistosomiasis control. A few health workers perform symptom-based treatment and also have praziquantel in stock. From the current study it is clear that for the Ministry of Health in Ghana to proceed with policy to integrate schistosomiasis control, several challenges have to be addressed. Following a similar study in Northern Senegal (Van der Werf *et al.*, 2002b), it proved possible to reach high levels of symptom-based treatment and availability of praziquantel as a result of special interventions including training of staff and improvement in the dissemination of praziquantel. Also in Mali, where emphasis on integrated schistosomiasis control has existed for many years, the results are promising (A. Landouré, personal communication). For Ghana, wider availability of praziquantel in endemic areas and training of staff to improve case recognition as well as case management are the most important requirements.

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7

Evaluation of case management in the integrated schistosomiasis control programme in Mali

Landouré, A., Van der Werf, M. J., Traoré, M. and De Vlas, S. J. Evaluation of case management in the integrated schistosomiasis control programme in Mali. Submitted

Abstract

Currently, schistosomiasis control in Mali is mainly based on treatment with praziquantel. The policy is to ensure treatment of school-aged children every three years in all areas where the prevalence of haematuria in this age group is above 30%; and a proper management of all patients presenting with haematuria or (bloody) diarrhoea at health centres. We evaluated the application of case management by visiting 60 health care facilities in four geographical areas and interviewing the health workers of the facilities. *Schistosoma haematobium* was reported to be present in the coverage area of 83% and *S. mansoni* in 37% of the health care facilities.

Patients presenting with symptoms related to schistosome infection are very likely to receive adequate treatment, esp. for haematuria caused by *S. haematobium* (≈ 80%). Most health workers appeared to know the main symptoms caused by schistosome infection. At health centre level patients were often directly treated with praziquantel (PZQ), whereas in district hospitals and private clinics health workers first requested a diagnostic test. PZQ was available in most health care facilities but not in the private clinics. Treatment of *S. haematobium* infection costs on average 2.30 Euro, which is comparable to the treatment costs of *S. mansoni*, 2.37 Euro. The cost of PZQ represented approximately 50% of the total cost borne by the patients when presenting at health centres.

We conclude that, patients with symptoms of *S. haematobium* infection in Mali can expect adequate diagnosis and treatment in agreement with the WHO recommendations. Patients presenting with symptoms related to *S. mansoni* infection are less likely to be correctly diagnosed. The high cost of treatment but also the low tendency to seek health care necessitate policy decisions to ensure an affordable and more attractive clinical case management system.

Introduction

Schistosomiasis is a serious public health problem in Mali. It affects one in every 4 individuals. The high prevalence and intensity of infection result in significant morbidity and growth impairment in children (Traoré *et al.*, 1998a, Traoré *et al.*, 1998b, De Clercq *et al.*, 1998). Over the past decades, a national survey and other specific studies were conducted by the National Schistosomiasis Control Programme (PNLCS). The main endemic areas were identified and control strategies defined, (Traoré, 1989, Werler, 1989, Traoré *et al.*, 1998a).

Control efforts started in 1978 with a research and control project based at the National Institute for Public Health Research (INRSP) in Bamako. Activities were planned on a pragmatic basis depending on survey results and logistic conditions. In 1982, a national schistosomiasis control programme started, which aimed at morbidity control by vector control and population mass chemotherapy with praziquantel delivered by mobile teams operating from their basis in Bamako (Seubert *et al.*, 1977, Brinkmann *et al.*, 1988). After evaluation of this project in 1987, it was recognised that the vertical approach was difficult to maintain due to the high costs (Gryseels, 1987). This initiated efforts to integrate control activities in primary health care structures as recommended by WHO (WHO, 1985). A central team responsible for co-ordination, surveillance and research was appointed at the INRSP, whereas implementation of control interventions was transferred to the district and regional health team. The current control strategy is to treat school aged children repeatedly every three years in moderate to high endemic areas and more importantly to establish adequate clinical care for patients presenting at health care facilities in all endemic areas (i.e. passive case detection) by strengthening the health system. A decision tree was adopted for the management of patients with haematuria or bloody diarrhoea that visit health centres in schistosome endemic areas. The strategy included direct treatment with praziquantel for patients presenting with haematuria, whereas for patients presenting with bloody diarrhoea a laboratory test should be requested for confirmation of the diagnosis. This required continuous availability of praziquantel at health centre level and laboratory facilities to perform the Kato-Katz technique for diagnosis of *S. mansoni* eggs. Between 1987 and 1998, one medical doctor, several nurses and all laboratory technicians in endemic and non-endemic districts, were trained in diagnosis (urine filtration, Kato-Katz technique, use of reagent strips) and treatment of schistosomiasis patients and a supply of reagent strips, and materials for urine filtration and Kato-Katz technique was provided to the laboratories.

More than a decade after the start of the integration process, we evaluated the functioning of the health care facilities for passive detection and treatment of *S. haematobium* and *S. mansoni* cases. The process included interview of the health workers to assess their knowledge of the main symptoms and their attitude and practice for diagnosis and treatment of schistosomiasis; the availability of diagnostic materials and praziquantel was also recorded.

Methods

Malian District Health System

The health system in Mali is based on the principles of Primary Health Care and the Bamako Initiative (WHO, 1978, Garner, 1989). The first level of care in the health system is at the Centre de Santé Communautaire (CSCOM) or Centre de Santé Revitalisé (CSAR). In rural areas, these are generally situated at village level and provide a minimum package of preventive and curative services to the population living in the coverage area. Normally, each health centre is staffed with one senior nurse (Infirmier d'Etat) or one nurse (Infirmier de santé) and two assistant nurses (aide soignant and matrone). Patients that cannot be handled at the level of the CSCOM are referred to the next level, i.e. the district hospital (Centre de Santé de Réfèrence = CSREF). These employ at least one medical doctor and several senior nurses, nurses and assistant nurses. The medical doctor of the district hospital supervises the activities of the health centres located in the district. A district contains a district hospital, 4 to 8 health centres and one or more private clinics in some areas.

For each visit to a health care facility, patients buy consultation tickets. They also pay for drugs and diagnostic tests if necessary. Health centres buy generic drugs at the Regional Pharmacy. The retail price of the drug and the type and quantity in stock are determined by the health worker in command of the health centre and the health committee, a group of representatives chosen from the local population. The health centres make a small profit by selling the drugs to patients, which enables them to renew their stocks and to support salaries of some health workers (cost recovery system based on Bamako Initiative). Patients can also buy drugs at private pharmacies.

Study area

The study was performed in November and December 2001 in four regions in Mali with different levels of schistosomiasis endemicity. Figure 7.1 shows the surveyed districts, a district with low endemicity was Kolondiéba (Sikasso region) and high endemic districts were Kolokani and Banamba (Koulikoro region), Niono (Ségou region) and Bandiagara (Mopti region) (Werler, 1989, Kardorff *et al.*, 1994, Vercruysse *et al.*, 1994, De Clercq *et al.*, 1995, De Clercq *et al.*, 1997, Traoré *et al.*, 1998a). From each region, two districts were included in the study. In the first visited district, we selected the district hospital and randomly, one private clinic (if present) and 13 or 14 health centres until a total of 15 health care facilities. If less than 15 health care facilities were present in the first district, all were included and we randomly selected health care facilities in the second district until a total of 15 health care facilities were included.

Data collection

We used the structured questionnaire which was developed for a comparable study in Senegal (Van der Werf *et al.*, 2002b). It contained questions on knowledge of symptoms

and treatment of schistosomiasis and on the availability and cost of drugs and diagnostic tests. In addition, four hypothetical cases were presented to assess the case management process of patients with typical schistosomiasis symptoms (case A: 10 year old girl with blood in urine; case B: 40 year old man with blood in urine and painful urination; case C: 10 year old boy with abdominal discomfort and bloody diarrhoea and case D: 30 year old woman with diarrhoea and abdominal discomfort).

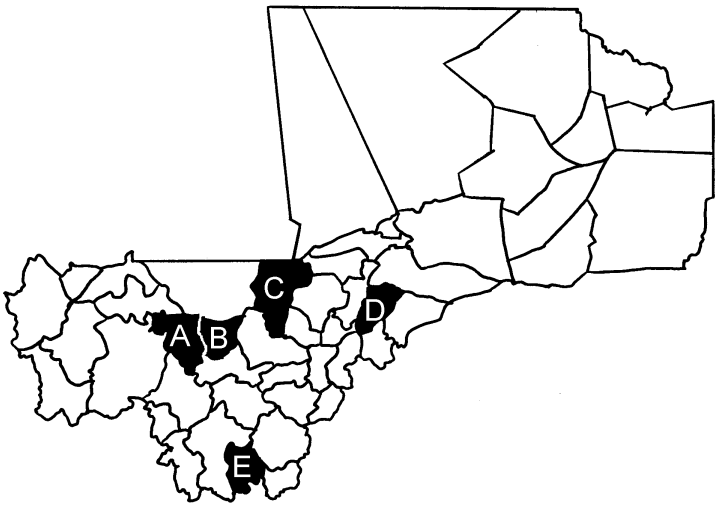

Figure 7.1: Map of Mali indicating surveyed districts: (A) Kolikani, Koulikoro Region; (B) Banamba, Koulikoro Region; (C) Niono, Ségou Region; (D) Bandiagara, Mopti Region and (E) Kolondiéba, Sikasso Region.

The person in charge of each surveyed health care facility was interviewed. If this person was absent, we interviewed the second in command. We explained that the purpose of the questionnaire was to evaluate the functioning of the health care facility. So we did not reveal the specific aim of our study: to evaluate the functioning of the health care facility for schistosomiasis control. After introduction and some general questions about the health care facility, we presented the four hypothetical cases in random order. Respondents were requested to imagine that these cases visited their health care facility and to explain their usual policy for such patients taking into account the epidemiological characteristics of the population in their coverage area and the diagnostic and therapeutic possibilities available in their health care facility. Thereafter, we explained the purpose of our visit and focussed the interview on schistosomiasis. Respondents were asked to mention all symptoms they considered to be related to infection with *S. haematobium* or *S. mansoni*. If *S. haematobium* or *S. mansoni* infection was reported present in the coverage area of the health care facility, we continued the interview with questions about diagnosis and treatment practices for patients presenting with symptoms caused by *S. haematobium* (haematuria) and *S. mansoni* infection (blood in stool/bloody diarrhoea). Subsequently, we asked them which percentage of their coverage population would first consult a traditional

healer before visiting their health care facility for the symptoms haematuria and bloody diarrhoea. Thereafter, we determined the availability of diagnostic materials and praziquantel. We collected information about the number of people covered by the health care facility, the number of curative consultations, the number of schistosomiasis patients in 2000 and the price of a consultation ticket, diagnostic test, praziquantel and public transport to the nearest referral centre. For all questions we tried to obtain the exact value, if this was not possible an estimated value was asked for. In some instances, information was provided by mail or telephone up to a few days after the interview.

If the respondent did not know schistosomiasis or if it was unknown whether schistosomiasis was present in the coverage area, the data were analysed as not having schistosomiasis in the coverage area. The replies given by different professional groups or primary health care levels were statistically compared using the Chi-square/Fisher's exact test (SPSS). A p-value < 0.05 was considered significant.

Cost analysis

Calculation of the average costs of treatment is described by Van der Werf et al. (2002b). Briefly, costs of treatment for schistosomiasis were calculated by adding the price of consultation ticket, diagnostic test, treatment with four praziquantel tablets (dose for an adult) and transportation cost to another health care facility. If a diagnostic test is not requested costs are nil. Also, if patients are not referred for diagnostic test or treatment transportation costs are nil. All costs are presented in Euro. In 2001, one Euro was approximately 650 CFA (local currency).

Results

Table 7.1 summarises the population covered by the 60 surveyed health care facilities and their number of curative consultations in the year 2000. We interviewed in the district hospitals six medical doctors, in health centres one medical doctor, 20 senior nurses, 20 nurses and 10 assistant nurses and in private clinics one medical doctor, one senior nurse and one nurse. *S. haematobium* infection was reported to occur in the coverage area of 50 (83%) health care facilities, 22 (37%) also reported *S. mansoni*. Two (3%) respondents did not know whether *S. mansoni* infection existed in their coverage area.

Table 7.2 lists general characteristics of the health care facilities in our study. Hospitals employed several medical doctors, whereas health centres were mainly staffed by nurses. All three hospitals had an in-patient department with on average 46 beds. Health centres and private clinics only had few beds which were mainly used for short-term observation. Laboratories were almost exclusively available at district hospital level. They were in the possession of all necessary equipment for urine centrifugation (microscope, tubes, glass-slides and centrifuge) and direct smear tests (microscope and glass-slides) to diagnose *S. haematobium* eggs and *S. mansoni* eggs respectively. Urine filtration tests and Kato-Katz tests

Table 7.1: Characteristics of the 60 visited health care facilities (HCF) in Mali.

Health care facility	No.	Population covered by HCF in thousands, median (range)*	Number of curative consultations year 2000 in thousands, median (range)**	No. of HCF reporting presence of schistosomiasis in their coverage area (%)***	
				S. haematobium	*S. mansoni*
District hospital	4	212 (152–257)	6.2 (2.3–27)	4 (100%)	2 (50%)
Health centre	53	12 (3.3–53)	1.8 (0.64–5.5)	43 (81%)	18 (34%)
Private clinic	3	n.a.*	0.37 (0.25–2.6)	3 (100%)	2 (67%)
Total	60			50 (83%)	22 (37%)

* n.a. = not applicable, private clinics do not have a specified coverage area

** Six health centres did not practice the whole year of 2000 and were therefore not included

*** All health care facilities with *S. mansoni* also had *S. haematobium* in coverage area

were not used and the necessary materials were only available in one district hospital (Kolondiéba district). Most non-private health care facilities with reported schistosomiasisin the coverage area had praziquantel available at the time of the interview (83%). They had on average 137 tablets in stock (range 7-557). None of the three private clinics had a dispensary or praziquantel. In Mali, most *S. haematobium* patients were diagnosed and treated at health centre level, approximately 1500 in our sample in the year 2000, 100 in district hospitals and 50 in private clinics. *S. mansoni* patients were not separately registered in the Malian health system.

Table 7.2: Availability of personnel and equipment in 50 Malian health care facilities with reported schistosomiasis (both *S. haematobium* and *S. mansoni* or only *S. haematobium*) in their coverage area.

	Health care facility		
Available	District hospital (n=4)	Health centre (n=43)	Private clinic (n=3)
Staff, median (range)			
Doctors	4.5 (3–7)	0 (0–1)	0 (0–1)
Senior nurse	4.5 (1–6)	0 (0–2)	1 (0–2)
Nurses	3 (1–3)	1 (0–2)	1 (0–2)
Nurse help	4 (1–6)	2 (1–4)	0 (0–1)
Facilities, number (percentage)			
Laboratory	4 (100%)	2 (5%)	0 (0%)
Praziquantel	4 (100%)	35 (81%)	0 (0%)

The majority of the respondents mentioned urinary schistosomiasis as initial diagnosis for hypothetical cases A and B, respectively 92% and 57%. In contrast, case D and to a lesser extent case C was hardly ever given the initial diagnosis of (intestinal) schistosomiasis (Case C: 15% and Case D: 2%). If the four cases really concerned schistosomiasis patients, the ultimate probability of prescribing proper treatment (praziquantel) for cases A, B, C and D without referral would be 87%, 62%, 23% and 10%, respectively, provided a positive diagnosis test if requested. Health workers from areas reported endemic for schistosomiasis more often prescribed praziquantel (Table 7.3). In these areas, only three

health centres did not prescribe praziquantel for hypothetical case A, although one of them did have urinary schistosomiasis as initial diagnosis. Also, nine health centres and one private clinic did not prescribe praziquantel for case B. Their initial diagnosis was bacterial urinary infection (60%) and gonorrhoea (40%), which explains the prescription of antibiotics. For case C and D health centres prescribed praziquantel directly while all district hospitals only prescribed praziquantel after a positive diagnostic test.

Table 7.3: Diagnosis and treatment strategy for 4 hypothetical cases in health care facilities with reported *S. haematobium* or *S. mansoni* in their coverage area. Hypothetical cases: 10 year old girl with blood in urine (Case A); 40 year old man with blood in urine and painful urination (Case B); 10 year old boy with abdominal discomfort and bloody diarrhoea (Case C); and 30 year old woman with diarrhoea and abdominal discomfort (Case D).

	S. haematobium (n=50)		*S. mansoni* (n=22)	
	Case A (%)	Case B (%)	Case C (%)	Case D (%)**
Initial diagnosis schistosomiasis	47 (94)	32 (64)	9 (41)	1 (5)
Action				
Direct prescription of praziquantel	40 (80)	28 (56)	7 (32)	2 (9)
Prescription of praziquantel if schistosome eggs found in diagnostic test*	6 (12)	8 (16)	4 (18)	4 (18)
Direct prescription of other drug#	3 (6)	10 (20)	11 (50)	15 (68)
Referred for diagnosis and/or treatment	1 (2)	4 (8)	0 (0)	0 (0)

* Diagnostic tests were urine centrifugation (*S. haematobium*) and direct smear (*S. mansoni*)

** One respondent waited for two days to see if the symptoms would disappear

Mainly antibiotics, metronidazole and ORS

Almost all health workers (98%) mentioned haematuria when asked to report symptoms related to *S. haematobium* infection (Figure 7.2a). Respectively 63% and 47% also reported dysuria and pelvic pain. Symptoms less commonly or not associated to *S. haematobium* infections, fever, pruritis, and anorexia, were sometimes mentioned. There was no significant difference in (the quality of) the answers between highly qualified health workers (doctors and senior nurses) and other health workers (nurses and assistant nurses). Also, answers of health workers from areas with reported *S. haematobium* were comparable to answers of those from areas without reported *S. haematobium*. Most health workers from health centres (88%) in areas with reported *S. haematobium* performed symptom-based treatment (i.e. treatment without parasitological confirmation of the diagnosis) for patients with haematuria (Table 7.4). Whereas all doctors working in district hospitals first requested a diagnostic test before they prescribed praziquantel. In private clinics, patients were always referred for a diagnostic test. Praziquantel was prescribed by 98% of the respondents for treatment of *S. haematobium* infection, most of them prescribed 40 mg/kg bodyweight (92%), 2 (4%) prescribed 25 mg/kg and 2 (4%) did not prescribe per kilogram bodyweight.

The main symptoms of *S. mansoni* infection, abdominal discomfort and bloody diarrhoea/blood in stool, were mentioned by 78% and 60% respectively, when asked to

Table 7.4: Management of patients reporting with haematuria or blood in stool/bloody diarrhoea in health care facilities where the health worker mentioned the symptoms as signs of respectively *S. haematobium* and *S. mansoni* infection in areas where *S. haematobium* or *S. mansoni* is reported endemic. Positive for diagnosis means *S. haematobium* eggs detected in urine sample or *S. mansoni* eggs detected in stool sample.

	Health care facility (%)		
	Hospital	Health centre	Private clinic
Haematuria			
Symptom-based treatment with praziquantel*	0 (0)	38 (88)	0 (0)
Diagnosis by urine centrifugation, if positive praziquantel	4 (100)	2 (5)	0 (0)
Referral for diagnostic test, if positive praziquantel	0 (0)	3 (7)	3 (100)
Total	4 (100)	43 (100)	3 (100)
Bloody diarrhoea/blood in stool			
Symptom-based treatment with praziquantel**	0 (0)	9 (64)	0 (0)
Diagnosis by direct smear, if positive praziquantel	2 (100)	1 (7)	0 (0)
Referral for diagnostic test, if positive praziquantel**	0 (0)	4 (29)	2 (100)
Total	2 (100)	14 (100)	2 (100)

* One respondent prescribed mebendazole

** One respondent prescribed metronidazole

report symptoms related to *S. mansoni* infection (Figure 7.2b). Other symptoms related to *S. mansoni* infection were rarely mentioned. Eight percent of the respondents could not mention any symptom related to *S. mansoni* infection at all. Highly qualified health workers (doctors and senior nurses) gave similar answers about *S. mansoni* symptoms compared to other health workers (nurses and nurse helps). The answers of health care workers from areas where *S. mansoni* was reported to be present were significantly better for the symptoms abdominal discomfort and bloody diarrhoea/blood in stool

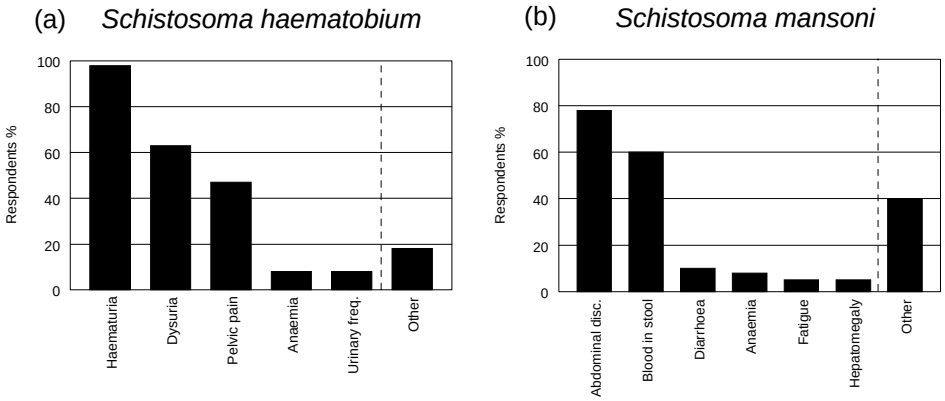

Figure 2: Symptoms mentioned by respondents (n = 60) to be related to (a) *S. haematobium* and (b) *S. mansoni* infection. Respondents were requested to mention as many symptoms related to schistosomiasis as possible. Five (8%) health workers could not mention any symptom caused by *S. mansoni* infection. Urinary freq. is urinary frequency. Abdominal disc. is abdominal discomfort. "Other" refers to symptoms less commonly associated with schistosomiasis. In order of importance, these were fever, pruritis, anorexia, kidney pain, and hepatosplenomegaly for *S. haematobium*, and pruritis, dizziness, anal pain, constipation, itching in anal region, fever, vomiting, haematuria, and anorexia for *S. mansoni.*

(p = 0.021 and p= 0.013). Symptom-based treatment for patients presenting with bloody diarrhoea/blood in stool was performed by 4 senior nurses, 3 nurses and 2 assistant nurses working in health centres. All prescribed praziquantel at 40 mg/kg bodyweight, except one nurse who prescribed metronidazole. Two doctors working in district hospitals and two health workers from private clinics requested a diagnostic test before prescribing praziquantel.

The cost of a consultation ticket was substantially higher in district hospitals and private clinics compared to health centres (Table 7.5).

Table 7.5: Mean costs of registration, diagnostic test, treatment and transportation for referral in different types of health care facilities. If the health worker reported to refer patients for a diagnostic test or for buying praziquantel, the costs of a diagnostic test and/or praziquantel in the referral centre were used. If health workers referred to a health care facility outside the study sample or private clinic/pharmacy, we used the mean costs of a diagnostic test or praziquantel in hospitals. Transportation costs are nil for patients that were not referred for diagnostic test or treatment. Costs of diagnostic test are nil if a diagnostic test was not requested. 100 CFA = 0.15245 Euro.

	Health care facility			
	District hospital	Health centre	Private clinic	All
S. haematobium reported in area*	4	40	3	47
Consultation ticket	1.72	0.39	1.37	0.57
Urine centrifugation	0.90	0.13	1.07	0.26
4 praziquantel tablets	1.23	1.27	1.24	1.26
Transportation to other HCF	0.00	0.25	0.00	0.21
Total costs	3.85	2.04	3.68	2.30
S. mansoni reported in area**	2	17	2	21
Consultation ticket	1.52	0.37	0.53	0.50
Direct smear	0.65	0.15	0.65	0.25
4 praziquantel tablets	1.25	1.26	1.27	1.26
Transportation to other HCF	0.00	0.45	0.00	0.36
Total costs	3.42	2.23	2.45	2.37

* Three health centres with incomplete data were excluded
** Not included: data from 1 health centre that prescribed metronidazole for treatment

To increase accessibility there was an exemption system. Schoolchildren did not pay for a consultation ticket in 19 health centres and 2 district hospitals. In 5 health centres (all in Koulikoro region) the price of the consultation ticket was half for schoolchildren. Elderly people were exempted from buying a consultation ticket in 7 health care facilities. Other exemptions were militaries (1 health centre) and paupers (2 health centres). The mean costs of diagnostic tests were higher in district hospitals and private clinics. This was mainly due to the use of symptom-based treatment in most health centres. The real cost of a diagnostic test (i.e. excluding the health care facilities where a diagnostic test was not requested) was comparable between district hospitals and health centres. It was on average 1.07 Euro (range 0.61–2.13) for a urine centrifugation test and 0.66 Euro (range 0.61–0.69) for a direct smear test. Also, the average price of praziquantel was comparable between district hospitals and health centres, respectively 0.31 Euro and 0.32 Euro per

tablet (600 mg). The costs of praziquantel for an adult (4 tablets) constitute approximately 50% of the overall costs of treatment.

Discussion

Our study shows that the majority of the health workers had the knowledge necessary for identification of *S. haematobium* patients and was familiar with the recommended treatment. This was confirmed by the results of the hypothetical cases. Following the objectives of the PNLCS and the WHO recommendations to integrate schistosomiasis control in primary health care facilities (WHO, 1993), most health centres have adopted the strategy of direct treatment for patients presenting with haematuria. All health care facilities with a laboratory use a diagnostic test to confirm the symptom-based diagnosis. As praziquantel is widely available, we can safely conclude that most patients with symptoms related to *S. haematobium* infection could receive proper treatment when they present at the health system. However, studies done in several settings, (Taylor *et al.*, 1987, Kamunvi and Ferguson, 1993, Amazigo *et al.*, 1997, Aryeetey *et al.*, 1999), showed that in many endemic areas, schistosomiasis is not considered as a serious disease. This was also confirmed by a recent study in Mali (Landouré, personal communication). The low perceived seriousness of the symptoms possibly results in a small number of individuals seeking health care for symptoms related to *S. haematobium* and *S. mansoni* infection; only 50% of individuals with *S. haematobium*-related clinical manifestations present spontaneously at health centres. The PNLCS and the National Centre for Education Information and Communication (CNIECS) are planning workshops at regional and district level for health personnel and staff of water development sectors in order to improve the knowledge, attitude and practices on the prevention and control of schistosomiasis and increase health care seeking for schisosomiasis. Local radios will also be used to broadcast health education messages.

The results of the hypothetical cases confirmed that patients presenting with symptoms related to *S. mansoni* infection are less likely to be diagnosed as intestinal schistosomiasis case and to receive treatment with praziquantel. This is probably due to the fact that bloody diarrhoea and abdominal discomfort are not specific for *S. mansoni*. The hypothetical cases were often considered to be caused by another disease (e.g. amoebiasis). The regional and district training workshops will address this issue in emphasising the application in schistosomiasis endemic areas of systematic treatment of patients presenting at health centres with bloody diarrhoea and abdominal discomfort, initially with PZQ, and subsequent referral to district level in case of non response to treatment. However, the cost of referral for a diagnostic test is substantially high, (0.45 Euro). There is a need for policy decision to be made in order to make diagnostic and treatment at health centres cheaper and more attractive to individual with clinical manifestations.

All in all, symptom-based direct treatment is considered the most suitable strategy for health workers in rural health centres. As most schistosomiasis patients are treated at health centre level in Mali, direct treatment is the most frequently applied case management strategy. The PNLCS in an action plan for the next 5 years is planning to

improve this strategy with the application of reagent strip testing for haematuria at Community Health Centres, where laboratory facilities are not available. Previous studies in mixed *S. haematobium* and *S. mansoni* infection areas in Mali showed that more than 90% of individuals infected with *S. mansoni* are also infected with *S. haematobium* (Traoré, 1994). Treatment of individuals found positive at reagent strip testing for microheamaturia is considered as an efficient way to control both urinary and intestinal schistosomiasis in the Malian context. A system is been put in place by the PNLCS to monitor the impact of this strategy.

WHO recommends the use of urine sedimentation, centrifugation or filtration for laboratory diagnosis of *S. haematobium* infection and the Kato Katz method for diagnosis of *S. mansoni* (WHO, 1993). Accordingly, the PNLCS has trained laboratory technicians in the urine filtration technique for *S. haematobium* diagnosis and the Kato-Katz method for *S. mansoni* diagnosis and provided supplies of the necessary materials in the 1990s. Our study showed that several years after the end of the training, none of the laboratories were using the recommended diagnostic methods and diagnostic materials were left unused on the shelves. Instead, the technicians preferred the urine centrifugation test for *S. haematobium* eggs and the direct smear test for diagnosis of *S. mansoni* eggs. The main reasons given are the extra time needed to perform urine filtration and Kato-Katz technique as compared to direct examination, the relatively high cost of the materials and the limited sensitivity for detecting other pathological changes. However, the Kato-Katz and the urine filtration techniques are more sensitive for the identification of schistosome eggs; direct examination of urine and stool samples leave a high proportion of infected individuals undiagnosed. The PNLCS considers the application of the urine filtration test and the Kato-Katz method as a must for the diagnosis of schistosomiasis at district level. The PNLCS has planned to make test materials available at affordable price in all districts and conduct continuous training and supervision on the quality of test performance.

Praziquantel was available in most health care facilities indicating that the majority of the local health committees felt that the drug is important and should be in stock and that the supply system by the National and Regional pharmacies was reliable. The few health care facilities where praziquantel was not available had none or only few registered schistosomiasis patients in the year 2000. They preferred to refer their patients to a private pharmacy due to the low profit margin on praziquantel and limited expiry time. The cost of praziquantel was relatively high (1.26 Euro) and made up 50% of the total costs. During the early phase of schistosomiasis control, praziquantel was regularly distributed free of charge by the PNLCS in order to cover a large proportion of the population (until 1990). Thereafter it was included in the cost-recovery system. It is unknown whether this has affected the number of individuals being treated as has been reported for other diseases in Ghana (Waddington and Enyimayew, 1989, Biritwum, 1994).

The total cost of treatment for schistosomiasis (registration, diagnostic test and drugs) seems considerable given the GNP of USD 240 per capita in the year 2000 in Mali (IMF country report No. 02/1, January 2002). This could have a negative influence on the

access of treatment. Patients might prefer to visit traditional healers, as reported by the health workers in our study. They estimated that for complaints related to schistosome infection, such as haematuria and bloody diarrhoea, a large proportion of patients (60%) probably first visited a traditional healer before contacting the health care facility. As praziquantel is the only effective drug currently available for the treatment of schistosomiasis, seeking first the treatment of traditional healers will delay proper cure at health centres.

In conclusion, after a considerable effort to integrate schistosomiasis control in Mali, passive case detection by the health system is functioning satisfactorily, especially for *S. haematobium*. The situation in Mali is comparable to that in Northern Senegal at the end of a European Union supported programme to improve schistosomiasis control (Van der Werf *et al.*, 2002b) and much better than in Ghana where a national schistosomiasis control programme does not exist (Van der Werf *et al.*, in press-a). There is a need for continuous training of health personnel for a full understanding and a rigorous implementation of the symptom-based treatment approach combined with the application of reagent strip testing for micro-haematuria as a minimum package of care at all Community Health Centres. Urine filtration and the Kato-Katz technique should remain standard diagnostic techniques at district level.

The availability of praziquantel at affordable price and the implementation of a proper health education programme are necessary accompanying measures. As cost is the key issue, the PNLCS is preparing an action plan proposing that diagnosis and treatment with praziquantel should be free for school-aged children, the most affected and the target group for morbidity control. A policy decision needs to be made on who should bear the cost of this strategy.

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8

Evaluation of staff performance and material resources for integrated schistosomiasis control in Northern Senegal

Van der Werf, M. J., Mbaye, A., Sow, S., Gryseels, B. and De Vlas, S. J. (2002). Evaluation of staff performance and material resources for integrated schistosomiasis control in Northern Senegal.. *Tropical Medicine and International Health*, **7,** 70-79.

Abstract

BACKGROUND: A project to improve integrated control of schistosomiasis in the primary health care system of Northern Senegal was implemented from February 1995 until September 1999, shortly after a *Schistosoma mansoni* outbreak. The activities included additional training of doctors and nurses in symptom-based treatment and making praziquantel (PZQ) available for an affordable price.

OBJECTIVE: To investigate staff performance and the availability and costs of diagnostic materials and PZQ at the end of this intervention project.

METHODS: We performed structured interviews with staff from 55 health care facilities in five districts.

RESULTS: Respondents from 23 health care facilities reported both *S. haematobium* and *S. mansoni* in the coverage area, 32 reported only *S. haematobium* and three only *S. mansoni*. The average costs to patients for consultation, diagnosis, treatment and transportation to a referral health care facility were approximately 1.60 Euro. Fifty-seven per cent of the health care facilities with reported *S. haematobium* in the coverage area treated patients presenting with haematuria on symptoms; 56% of the health care facilities with reported *S. mansoni* in the coverage area treated patients presenting with blood in stool on symptoms. Thirteen per cent performed a diagnostic test for patients presenting with haematuria and 12% for patients presenting with blood in stool. The remainder, approximately one-third of the health care facilities, referred their patients to another facility for a diagnostic test. Implementation of symptom-based treatment in all health care facilities will reduce the total costs by 0.43 Euro (29%) for patients infected with *S. haematobium* and 0.78 Euro (46%) for patients infected with *S. mansoni*. Of the 53 health care facilities with schistosomiasis in their area, 37 had PZQ in stock of which 33 (88%) sold PZQ for the recommended retail price of 0.15 Euro per tablet (or 0.60 Euro per course of four tablets) or lower.

CONCLUSION: Four years after the start of the intervention project, patients presenting with schistosomiasis related symptoms can generally expect proper diagnosis and treatment at all levels of the health care system in Northern Senegal, either at the initial visited health care facility or after referral. However, a further reduction of the total costs of treatment is still possible by a better implementation of symptom-based treatment and further reduction of the costs of PZQ.

Introduction

The epidemiology of schistosomiasis in Northern Senegal has changed considerably in the past decade. Until 1986, *Schistosoma haematobium* was the only *Schistosoma* species reported in this area (Chaine and Malek, 1983, Vercruysse *et al.*, 1985). After the construction of two dams, Talla *et al.* (1990, 1992) reported an outbreak of *S. mansoni* infection in the district of Richard-Toll, Northern Senegal. The development of a high prevalence and intensity of infection within three years combined with frequent occurrence of early disease manifestations (abdominal pain and diarrhoea) (Stelma *et al.*, 1993, Stelma *et al.*, 1994, Stelma *et al.*, 1997, Picquet *et al.*, 1996, Kongs *et al.*, 1996) called for rapid and adequate control strategies. An increase in the prevalence of *S. haematobium* in the region of St Louis, Northern Senegal was also reported (Verlé *et al.*, 1994, Picquet *et al.*, 1996, Ernould and Ba, 1998).

Over the past decades, emphasis in schistosomiasis control has shifted to chemotherapy-based morbidity control (WHO, 1993). During the first years after praziquantel (PZQ) became available, this new strategy entailed mainly large-scale chemotherapy campaigns. The initial outcome of these vertical projects was a considerable reduction of infection rates and morbidity. However, the sustainability of these results was often disappointing, due to rapid re-infection and high costs (Gryseels, 1989). It became clear that there was a need for long-term strategies to achieve a lasting reduction of infection rates and morbidity. As vertical projects are expensive and difficult to maintain over long periods, WHO has recommended integrating schistosomiasis control in the primary health care structures (WHO, 1993). Access to drugs is a key element of a successful control program. In the WHO medicine strategy this is defined as rational selection and use of drugs, affordable prices, reliable supply systems and sustainable financing. Sustainable financing is assured in Senegal by a cost recovery system based on the Bamako initiative (Diallo *et al.*, 1993).

Based on experiences in the country and elsewhere, and according to national policies, the health authorities of Northern Senegal opted for maximum integration of schistosomiasis control in the existing health care structures. The initial strategy was passive case detection and treatment: i.e. patients who reported with intestinal symptoms possibly related to *S. mansoni* infection were prescribed PZQ or oxamniquine (Kongs *et al.*, 1994). At the beginning of the epidemic, patients could buy their medication at two private pharmacies for approximately US$ 25. However, these pharmacies often ran out of stock. After 1990, extra control measures were introduced to diminish the prevalence and morbidity caused by schistosomiasis, such as health education of the community and increasing the availability of PZQ in the area, and there were limited attempts to introduce snail control..

In February 1995, the Regional Health Authorities in St Louis started a programme, supported by the European Union, to improve schistosomiasis control in the area by strengthening of primary health care. The project mainly aimed at improving quality and accessibility of symptom-based treatment for schistosomiasis and health education at the community level. PZQ was made available at a reduced price at all levels of the primary

health care. Since January 1998, the Regional Health Authorities recommend a retail price of 0.15 Euro per PZQ tablet and a dose of 40 mg/kg bodyweight. However, health committees are free to implement the new price policy. Moreover, health workers were trained in diagnosis and treatment of schistosomiasis patients and equipped with microscopes and haemasticks. Nurses and sanitary agents working in high endemic areas were trained to treat schistosomiasis patients on symptoms: haematuria for *S. haematobium* and bloody diarrhoea, blood in stool or diarrhoea without fever and/or extreme paleness of the mucous membrane for *S. mansoni*. This strategy was included in the algorithms used by the nurses and sanitary agents. Furthermore, health education materials were prepared and applied with the aim to increase awareness of the symptoms of schistosomiasis and of the transmission cycle. There were four approaches: the development and distribution of educational materials to schoolchildren (in collaboration with the education sector), the production of an educational video film, the development and distribution of posters and billboards and broadcasting of radio programmes. Besides this, there were efforts by other sectors, such as programmes for water supply and the construction of latrines.

In this study, we evaluated the impact of the intervention project on curative health care. We determined the options for treatment and diagnosis and the knowledge of symptoms related to schistosomiasis infection at all levels of the health care system, evaluated the implementation of the price reduction for PZQ, determined the availability of diagnostic materials, counted the number of PZQ tablets available and calculated the total costs of treatment for the patient.

Methods

Study area

The study was conducted in May 1999, in the region St Louis in Northern Senegal (Figure 8.1), situated along side the Senegal River. The region is subdivided into five districts: St Louis (217,000 inhabitants), Richard Toll (119,000 inhabitants), Dagana (66,000 inhabitants), Podor (175,000 inhabitants) and Matam (256,000 inhabitants) (estimates for 1999).

Health system

The health services in Northern Senegal are organised according to the primary health care principle (WHO, 1978), which implies that health care facilities provide primary or secondary health care for a specified population. The number of people formally covered by the health care facility was reported by the person in charge.

Each district contains one health centre and a number of health posts, which varies from 10 to 39 depending on the size of the district. In each health centre there is at least one medical doctor in charge of all activities occurring within the health centre and in the health posts in the same district. The health posts are staffed with nurses or sanitary agents helped by nurse assistants. Their main task is providing simple primary care to their

coverage population. Cases which can not be handled at health posts are referred to the next level, the health centre. These are equipped to give curative and preventive services at primary care level. Complicated cases (including the long-term complications of schistosomiasis) are referred to the hospitals.

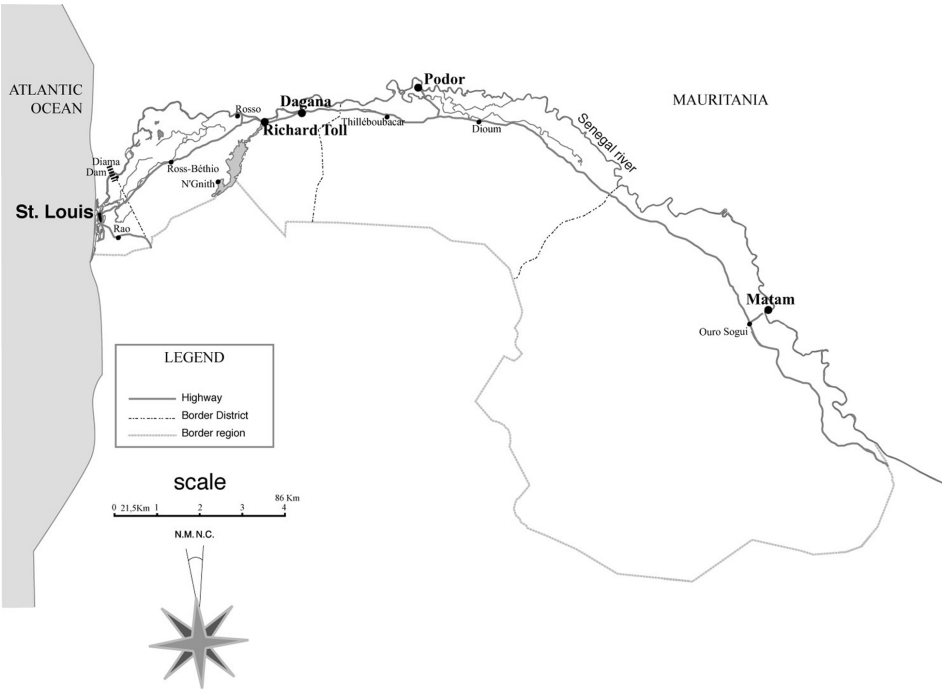

Figure 8.1: Map of study area, Northern Senegal

St Louis region has three hospitals: the regional hospital in the city of St Louis, a district hospital in Ndioum (Podor) and a district hospital in Ourossogui (Matam). The regional hospital in St Louis employs 12 medical doctors who provide secondary care, which includes general medicine, surgery, paediatrics, obstetrics and gynaecology, etc. It functions as the referral hospital for the entire population living in the region of St Louis, 833,000 inhabitants. The district hospital in Podor employs three doctors, the hospital in Matam, two. They provide simple secondary care to the total population of these districts. A health centre normally provides primary health care to the total population living in a district. However, due to the presence of the district hospitals in Podor and Matam, the health centres in these districts only cover the population living nearby. There are four private clinics in the district of St Louis, one in the district of Richard Toll and one in the district of Podor. Other health care facilities in the region of St Louis include Christian charity dispensaries and the health service of the sugarcane factory in Richard Toll. See Appendix for an overview of health care facilities visited.

In 1987, the Senegalese Ministry of Health introduced a cost recovery system for drugs according to the Bamako Initiative (Diallo *et al*., 1993). For Senegal this implied that health care facilities buy generic drugs at the National or Regional Pharmacy. They can make a small profit by selling the drugs to the patients, which enables them to renew their stocks. The retail price of drugs and the type of drugs in stock in the health care facility are determined by the (local) health committee, a group of representatives chosen from the (local) population.

Interviews and data collection

In the hospitals we interviewed the doctor in charge of the general medicine department, in health centres and private clinics the doctor in charge and in health posts the nurse or sanitary agent in charge. The knowledge of nurses and sanitary agents working in health centres and hospitals was not assessed. Respondents were asked to mention all symptoms they considered to be related to infection with *S. haematobium* or *S. mansoni*. If *S. haematobium* or *S. mansoni* infection was reported not present in the area of responsibility of the health care facility, further questions were not asked. If the infection was reported present, the interview continued with questions about the use of diagnostic tests and the prescription of treatment. The replies given by different professional groups were statistically compared using the Chi-square/Fisher's exact test (SPSS).

After the interview, we collected information on the number of schistosomiasis patients in 1998 and the total number of curative consultations in 1998. The number of PZQ tablets sold in 1998, the number of PZQ tablets currently in stock and the estimated number of days that PZQ was available in 1998 was recorded. At the end of the interview, we asked for the price of the consultation "ticket", the diagnostic test for schistosomiasis and a PZQ tablet. For all questions we tried to obtain the exact value, if this was not possible an estimated value was asked for.

Cost analysis

We calculated the total costs in Euro for treatment of schistosomiasis for each patient who visited the health care facility in 1998 by adding the price of a consultation ticket, a diagnostic test if requested and treatment with four PZQ tablets (dose for an adult). For health care facilities that reported to refer patients to another health care facility we took the price of a diagnostic test and PZQ at the centre of reference. The costs of a diagnostic test was considered to be nil in health care facilities that performed symptom-based treatment (i.e. no diagnostic test). If the interviewee referred patients to another health care facility for diagnosis and/or treatment, the estimated costs of transport to the centre of reference were included in the total costs. The costs of transport were provided by the local population. The Senegalese currency (CFA) was converted into Euro (in 1998, 1 Euro was approximately US$ 1 or CFA 650).

Results

The general characteristics of the included health care facilities are presented in Table 8.1. Only one nurse was not available for the interview (in Podor district). Twenty-three respondents reported the presence of both *S. haematobium* and *S. mansoni* infection in their area of responsibility, 27 reported only *S. haematobium* and three only *S. mansoni*. In only two health care facilities, both infections were reported absent (district St Louis: health post Tassinère and private clinic).

Table 8.1: Characteristics of the health care facilities (HCF) from which medical doctors, nurses or sanitary agents were interviewed.

Health care facility	No	Population covered by HCF, median (range)	No of consultations 1998 median (range)	Number of HCF reporting presence of schistosomiasis in its coverage area (%)	
				S. haematobium	*S. mansoni*
Hospital	3	256,000 (175,000-833,000)	46,000 (15,000-60,000)	3 (100)	1 (33)
Health centre	5	66,000 (9,000-217,000)	8,800 (1,500-17,000)	5 (100)	3 (60)
Health post	44	4,100 (500-30,000)	2,700 (400-12,000)	40 (91)	21 (48)
Private clinic	3	-*	2,300 (2,000-2,600)	2 (67)	1 (33)
Total	55			50 (91)	26 (47)

* No specified area of responsibility

Almost all interviewed persons mentioned the main symptoms of *S. haematobium* (haematuria, 100%) and *S. mansoni* infection (bloody diarrhoea and blood in stool, 94%) (Figure 8.2). Other symptoms caused by *S. haematobium* infection such as pelvic discomfort and dysuria were mentioned by, respectively, 56% and 33% of respondents. Seven nurses also reported "other" symptoms normally not related to *S. haematobium*, such as fever and nausea. Seventy-four per cent of the respondents mentioned abdominal discomfort as a symptom related to *S. mansoni* infection. Symptoms related to an advanced stage of the infection such as ascites and haematemesis were rarely mentioned. Four doctors and six nurses mentioned "other" symptoms that are usually assumed not to be associated with *S. mansoni* infection, such as fever, headache and dizziness.

Comparing the knowledge of the interviewed doctors (working in hospitals, health centres and private clinics) and the interviewed nurses and sanitary agents (exclusively working in health posts) revealed that knowledge was not significantly different except for pollakisuria which was more often mentioned by doctors, 36% *vs.* 2% (Fisher's exact $p = 0.004$). The knowledge of symptoms by nurses and sanitary agents did not depend on the reported presence of *S. haematobium* or *S. mansoni* infection in their area of responsibility (not shown).

In 67% of the health posts patients presenting with macroscopic haematuria were treated without parasitological confirmation of the symptom-based diagnosis (Table 8.2). Twenty-two (85%) of these health posts had PZQ available. Only one health centre performed symptom-based treatment and PZQ was available. For patients presenting with other symptoms related to *S. haematobium* infection both in health posts and in hospitals and health centres a diagnostic confirmation was always considered necessary.

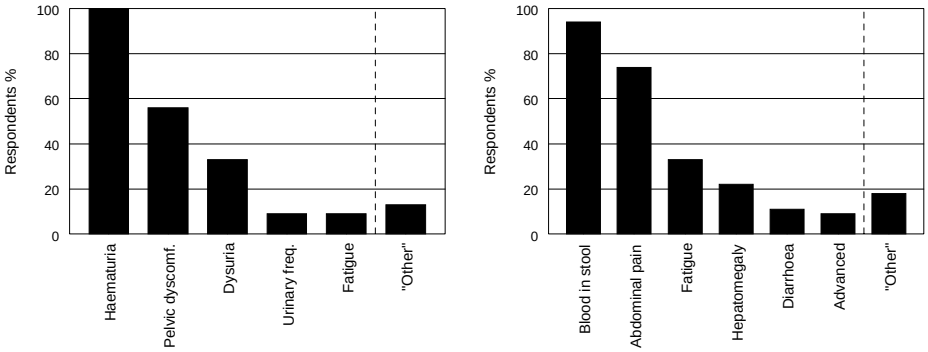

Figure 8.2: Symptoms mentioned by respondents to be related to *S. haematobium* and *S. mansoni* infection. *S. haematobium*: "Other" refers to symptoms usually not associated with *S. haematobium*: asthenia, headache, loss of weight, dizziness, vomiting, infertility and pruritis. *S. mansoni*: advanced = symptoms of advanced disease such as oedema, ascitis and haematemesis, "Other" refers to symptoms usually not associated with *S. mansoni*: fever, *ballonement abdominal* (bloated feeling, flatulence and swollen abdomen) and nausea.

Symptom-based treatment for *S. mansoni* infection (for blood in stool/bloody diarrhoea) was performed in 13 (62%) of the health posts and in one (25%) health centre in endemic areas (Table 8.2). PZQ was available in eight (62%) of these health posts and in also in the health centre. In Northern Senegal, all three hospitals had a laboratory; three of five health centres and six of 44 health posts had at least one microscope (Table 8.3). Other equipment necessary for a parasitological diagnosis of *S. haematobium* (urine filtration test: filters, syringes, tubes and glass-slides, urine centrifugation test: tubes, glass-slides and centrifuge) or *S. mansoni* (Kato-Katz method: mesh, template, cellophane/polyethylene coverslips, glycerine, malachite green and glass-slides, direct faecal smear: glass-slides) was available at health care facilities that reported to perform a parasitological diagnostic test. For parasitological diagnosis of *S. haematobium* infection, most laboratories performed the urine centrifugation test, sometimes in combination with the urine filtration test. In the districts of Podor and Matam where most *S. haematobium* cases are found (Chaine and Malek, 1983, Picquet *et al.*, 1996) more than 50% of the health care facilities were able to perform a diagnostic test (parasitological or haemastick) at the health care facility level.

Parasitological confirmation of *S. mansoni* infection was most often carried out with the direct faecal smear technique. More then 50% of the laboratory personnel reported to use the Kato-Katz technique if the direct faecal smear technique was negative. If a diagnostic

test was considered necessary and the facility did not have a laboratory or microscope, patients were referred to another health care facility. Doctors working in a private clinic always referred to a health centre or hospital for a diagnostic test. Reasons reported for not referring for a diagnostic test were high costs of a diagnostic test and the long journey to the nearest laboratory.

Table 8.2: Diagnosis and treatment strategy for patients reporting with haematuria or blood in stool and bloody diarrhoea in hospitals, health centres and health posts in areas endemic for *S. haematobium* and *S. mansoni*.

	Hospitals and health centres	Health posts
Haematuria		
Direct treatment with praziquantel	1 (12)	26 (67)
Diagnosis by haemastick	0 (0)	1 (3)
Diagnosis by urine filtration or centrifugation	5 (63)	0 (0)
Referral for diagnostic test	2 (25)	12 (30)
Total	8 (100)	39 (100)
Blood in stool & bloody diarrhoea		
Direct treatment with praziquantel	1 (25)	13 (62)
Diagnosis by direct smear or Kato-Katz	2 (50)	1 (5)
Referral for diagnostic test	1 (25)	7 (33)
Total	4 (100)	21 (100)

Values in parentheses are in percentages

Table: 8.3 Availability of laboratory and/or microscope, diagnostic materials and praziquantel in hospitals, health centres and health posts in Northern Senegal.

Available	Hospitals and health centres (n=8)	Health posts (n=44)
Laboratory and/or microscope	6 (75)	6 (14)
Material for parasitological diagnostic test *S. haematobium*[*]	6 (75)	1 (2)
Material for parasitological diagnostic test *S. mansoni*[**]	3 (38)	6 (14)
Praziquantel	6 (75)	33 (75)

Values in parentheses are in percentages

[*] Filters, syringes, tubes and glass-slides (urine filtration test) or tubes, glass-slides and centrifuge (urine centrifugation test)

[**] Mesh, template, cellophane/polyethylene coverslips, glycerine, malachite green and glass-slides (Kato-Katz method) or glass-slides (direct fecal smear)

PZQ (600 mg) was the only drug used in the programme in Northern Senegal for the treatment of *S. haematobium* and *S. mansoni* infection. The recommended dose of 40 mg/kg was prescribed by 75% of the hospitals and health centres and by 85% of the health posts. The other health care facilities prescribed 30 or 45 mg/kg bodyweight, and 10% of the nurses and sanitary agents did not know the recommended dose.

Seventy-five per cent of the hospitals, health centres and health posts had PZQ in stock at the time of the interview (Table 8.3). One hospital, one health centre and eight health posts with less than 25 schistosomiasis cases in 1998 did not have any because they always referred schistosomiasis patients to other health care facilities for treatment. More than 60% of the health care facilities with PZQ had >100 tablets in stock. Hospitals and health centres had PZQ every day in 1998. Of 34 health posts with PZQ available in 1998, 59% had it throughout the year. The duration of the periods that PZQ was reported unavailable in 1998 ranged from a few days to 330 days (median 40 days).

The mean price of a consultation ticket for adults in areas where *S. haematobium* infection is reported to be endemic was 0.22 Euro and in areas where *S. mansoni* infection is reported to be endemic 0.27 Euro (Table 8.4). The mean price of a test to diagnose *S. haematobium* eggs or haematuria, weighed for the number of patients and excluding the patients for which no diagnostic test was performed, was 0.66 Euro. The price of a urine centrifugation or filtration test ranged from 0.46 to 3.08 Euro, the haemastick test was less expensive, reported prices ranged from 0.00 to 0.31 Euro. The mean price of a diagnostic test for *S. mansoni* infection, was 0.68 Euro. The minimum price was 0.46, the maximum, 1.54 Euro. Eighty-eight per cent of health care facilities sold PZQ for the recommended price of 0.15 Euro. The maximum price for one PZQ tablet was 0.46 Euro in the district hospital of Matam. The mean price of four PZQ tablets in *S. haematobium* and *S. mansoni* endemic was comparable.

Table 8.4: Prices of consultation tickets, diagnostic tests and treatment in hospitals/health centres and health posts in Euro[*].

	Hospitals and health centres		Health posts		All	
	Real mean costs	Mean including zeros	Real mean costs	Mean including zeros	Real mean costs	Mean including zeros
S. haematobium area						
Consultation ticket adult	0.45	0.45	0.17	0.17	0.22	0.22
Four praziquantel tablets	0.92	0.92	0.80	0.80	0.82	0.82
Diagnostics	1.11	1.11	0.48	0.22	0.66	0.35
Transportation to other HCF	0.73	0.17	0.77	0.07	0.74	0.08
Total costs		2.65		1.27		1.48
S. mansoni area						
Consultation ticket adult	0.22	0.22	0.24	0.24	0.27	0.27
Four praziquantel tablets	0.82	0.82	0.64	0.64	0.63	0.63
Diagnostics	0.73	0.73	0.64	0.47	0.68	0.57
Transportation to other HCF	0.00	0.00	0.76	0.34	0.76	0.21
Total costs		1.66		1.69		1.68

[*] The mean price is a weighed average of the number of schistosomiasis patients visiting each health care facility in 1998. For facilities that neither performed diagnostic tests and nor referred patients for one, the costs of a diagnostic test was taken at 0 Euro. See Appendix for costs per health care facility.

Patients that were referred to another health care facility for a diagnostic test or for PZQ had to spend on average 0.75 Euro for transport. Most patients were referred for a

diagnostic test for *S. mansoni* (1666 patients in 1998). Less than 10% of the individuals with *S. haematobium* infection had to travel to another health care facility. The total costs (consultation ticket, diagnostic test, PZQ and transport to other health care facility) to patients infected with *S. haematobium* were on average 1.48 Euro (range 0.77–5.47). For patients infected with *S. mansoni* the average total costs were 1.68 Euro (range 0.77–3.94).

Discussion

Since 1993, the World Health Organisation has recommended a policy which aims at reducing the morbidity caused by *S. haematobium* and *S. mansoni* infection in highly endemic areas by integrating control in primary health care systems (WHO, 1993). This policy was also the main aim of the intervention project in the highly endemic area in Northern Senegal. The adequate knowledge of doctors, nurses and sanitary agents, the implementation of symptom-based treatment strategies (especially at health post level) and the wide availability of PZQ at a relatively low price are the main results of the intervention program. However, these results have been obtained by considerable investment of supervision time and capital. Whether they are sustainable remains to be seen.

Symptom-based treatment depends on sufficient knowledge of the main symptoms of schistosomiasis. In our study population, knowledge of the main symptoms of *S. haematobium* (haematuria) and *S. mansoni* infection (bloody diarrhoea/blood in stool) was satisfactory at all levels of the primary health care. However, despite the newly introduced policy to treat patients based on symptoms, more than half of the respondents still considered a laboratory test necessary. As more than half of the health posts did not have the laboratory equipment necessary for the parasitological diagnosis of schistosomiasis, a high percentage of patients had to be referred to another health care facility for a diagnostic test.

Symptoms related to an advanced stage of *S. mansoni* infection are rarely reported. So far only a small percentage of the population shows abnormalities on ultrasound investigation (Kardorff *et al.*, 1996, Kongs *et al.*, 1996, Yazdanpanah *et al.*, 1997, Burchard *et al.*, 1998). This might explain the underreporting of symptoms related to advanced disease by doctors, nurses and sanitary agents. As PZQ treatment can partially reverse the pathology of advanced disease (Boisier *et al.*, 1998, Frenzel *et al.*, 1999), rapid detection and treatment of these cases by improved knowledge of doctors, nurses and sanitary agents on these symptoms is important.

The first aim of the intervention project, lowering of the price of PZQ and increasing availability, appeared to have been widely realised. PZQ was widely available in the health care facilities 4 years after the start of the intervention programme. None of the health centres and hospitals had run out of stock and had a constant large supply in 1998. At health posts PZQ was available most of the time. Health committees decide what drugs should be available at their health care facility. Hence this may be an indication that

schistosomiasis is considered a priority by the committees. The special attention focussed on schistosomiasis in the area probably also influenced the decisions of the health committee. Another explanation for the high availability of PZQ might be that during the intervention project it was sometimes distributed for free, making it available to those facilities that would not normally stock it because they only diagnose a few schistosomiasis patients per year.

Part of the aim of the intervention project was to change the retail price by reducing the wholesale price of PZQ. The National/Regional pharmacy made PZQ available at a price of 0.13 Euro per tablet and the Regional Health Authorities recommended a retail price of 0.15 Euro. Therefore, health care facilities can still make a small profit, which enables them to replenish their stocks. Most health care facilities that participated in our study had introduced the new low retail selling price. A few health care facilities nevertheless sold PZQ at a higher price, reportedly because they needed to cover the costs for transport of the drug. The relatively low retail selling price of PZQ could have a strong positive influence on the access to treatment. However, although the recommend price of 0.15 Euro for one tablet is low compared with prices in other countries (Renganathan and Cioli, 1998), it still comprises almost half of the total costs of the treatment, which remains relatively high for a part of the (rural) population.

Implementation of all interventions according to the project will further reduce the total costs, especially symptom-based treatment. This eliminates the costs of diagnostic tests and the costs of (local) transport to another health care facility resulting in potential savings of 0.43 Euro (29%) for patients infected with *S. haematobium* (0.35 + 0.08 Euro) and 0.78 Euro (46%) for patients infected with *S. mansoni* (0.57 + 0.21 Euro) (Table 8.4). Applying the reduced retail price of PZQ in all health care facilities will lower the costs of treatment only by 0.22 Euro (mean price 0.82 instead of 0.60) for *S. haematobium* patients and by 0.03 Euro (0.60 rather than 0.63) for *S. mansoni* patients. To make the health system more accessible for schistosomiasis patients, the Regional Health Authorities should stress the importance of symptom-based treatment.

Ideally, evaluation of a project compares pre- and post-intervention data. In Northern Senegal, pre-intervention data were unfortunately not systematically collected. Thus we could only assess the situation at the end of the intervention project, and conclude that 4 years after the start of the programme the primary health care system is able to provide adequate and affordable diagnosis and treatment for the majority of patients reporting with schistosomiasis-related symptoms. It would be interesting to evaluate the sustainability of this intervention after some more years by using the same quantitative method.

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APPENDIX: Referral scheme and costs (Euro) for *S. haematobium* and *S. mansoni* diagnosis and treatment.

			S. haematobium			*S. mansoni*		
Health care facility	Costs of consultation ticket	Costs PZQ for adult[*,**]	Number of patients[***]	Costs of test[**]	Total costs for adult[#]	Number of patients[***]	Costs of test[**]	Total costs for adult[#]
St Louis								
1 Hospital St Louis	1.54	*(6)*	15	3.07	5.47	~	1.54	3.94
2 HC St Louis	0.46	*(6)*	25	*(1)*	4.39	5	*(1)*	2.86
3 HP Goxu Moth	0.15	*(6)*	**2**	*(1)*	4.08	-	-	-
4 HP Guett Ndar	0.15	*(6)*	5	*(1)*	4.08	12	*(1)*	2.55
5 HP Mbakhana	0.15	0.62	50	*(1)*	3.84	-	-	-
6 HP Poste Sud	0.15	0.86	**5**	*(1)*	4.08	-	-	-
7 HP Tassinere	0.15	-	-	-	-	-	-	-
8 PC St Louis	6.15	-	-	-	-	-	-	-
Richard-Toll								
9 HC Richard-Toll	0.31	0.62	**67**	0.77	1.70	**2067**	0.77	1.70
10 HP Boundoum Barage	0.31	0.62	**10**	[a]	0.93	**8**	*(9)*	1.70
11 HP Diawar	0.31	0.62	**9**	*(9)*	1.70	**236**	*(9)*	1.70
12 HP Gallo Malick	0.31	0.62	**8**	*(9)*	1.70	**816**	*(9)*	1.70
13 HP Nbagam	0.31	0.62	16	*(9)*	1.70	200	[a]	0.93
14 HP Ndiangue	0.31	0.62	-	-	-	**35**	*(9)*	1.70
15 HP Niassene	0.15	*(18)*	10	[a]	0.77	5	[a]	0.77
16 HP Ronkh	0.31	0.77	-	-	-	**468**	*(9)*	1.85
17 HP Rosso Senegal	0.31	0.62	**8**	*(9)*	1.70	**258**	[a]	0.93
18 HP Savoigne	0.31	0.62	**162**	0.46	1.39	**179**	0.46	1.39
19 HP Taouey	0.31	0.62	~	*(9)*	1.70	~	*(9)*	1.70
20 PC Richard-Toll	4.62	*(9)*	2	*(9)*	6.01	~	*(9)*	6.01

			S. haematobium			*S. mansoni*		
Health care facility	Costs of consultation ticket	Costs PZQ for adult[*,**]	Number of patients[***]	Costs of test[**]	Total costs for adult[#]	Number of patients[***]	Costs of test[**]	Total costs for adult[#]
Dagana								
21 HC Dagana	0.31	0.62	**58**	0.77	1.70	**188**	0.31	1.24
22 HP Bokhol	0.15	0.62	**211**	[a]	0.77	**239**	[a]	0.77
23 HP Dagana cite	0.15	0.62	**25**	*(21)*	1.54	**84**	*(21)*	1.08
24 HP Diagle	0.15	0.62	-	-	-	**174**	0.46	1.23
25 HP Gaya	0.15	0.62	**106**	0.08	0.85	**127**	0.46	1.23
26 HP Guidakhar	0.15	0.62	**7**	*(9)*	1.54	**166**	[a]	0.77
27 HP Mbane	0.15	0.62	**4**	[a]	0.77	**235**	0.46	1.23
28 HP Mbilor	0.15	0.62	**7**	*(21)*	1.54	**129**	[a]	0.77
29 HP Ndombo Diop	0.15	0.62	**6**	*(9)*	1.54	**166**	0.46	1.23
30 HP Niassante	0.15	0.62	**12**	*(21)*	1.54	-	-	-
31 HP Thiago	0.15	0.62	**11**	*(9)*	1.54	**175**	0.46	1.23
Podor								
32 Hospital Ndioum	0.46	0.62	50	1.54	2.62	-	-	-
33 HC Podor	0.31	0.62	~	0.46	1.38	-	-	-
34 HP Cascas	0.15	0.62	**53**	0	0.77	-	-	-
35 HP Dara Haleybe	0.15	0.62	**140**	0 *(32)*	0.77	-	-	-
36 HP Dounguel	0.15	*(32)*	5	*(32)*	2.31	**2**	*(32)*	~
37 HP Gollere	0.15	0.62	**6**	*(32)*	2.31	-	-	-
38 HP Mboumba	0.15	0.62	**30**	~	~	-	-	-
39 HP Mboyo	0.23	0.77	**115**	0	1.00	-	-	-
40 HP Ndiawara	0.15	0.62	**165**	0 *(33)*	0.77	-	-	-
41 HP Ndiayene Pendao	0.15	0.62	**18**	*(32)*	2.31	-	-	-
42 HP Walalde	0.15	[b]	~	[b]	~	-	-	-
43 PC Podor	0.31	*(33)*	250	*(33)*	1.39	-	-	-
Matam								
44 Hospital Ourossogui	0.77	1.85	85	0.77	3.39	-	-	-
45 HC Matam	0.15	0.62	**85**	*(44)*	1.54	-	-	-
46 HP Agnam Civol	0.15	0.62	**5**	0.31	1.08	-	-	-
47 HP Dembankane	0.15	1.23	240	[a]	1.38	-	-	-
48 HP Gaol	0.15	0.62	20	[a]	0.77	-	-	-
49 HP Goumal	0.31	0.62	**77**	0.15	1.08	-	-	-
50 HP Mil. Ourossogui	0	*(44)*	**23**	*(44)*	2.62	-	-	-
51 HP N'dendory	0.15	0.62	**186**	0	0.77	-	-	-
52 HP Ndiaffane	0.15	0.62	**9**	0.08	0.85	-	-	-
53 HP Ndouloumadji	0.15	0.62	**3**	0	0.77	-	-	-
54 HP Sinthiou Bamambe	0.15	1.23	400	0.15	1.53	-	-	-
55 HP Sinthiou Garba	0.15	0.62	30	0.04	0.81	-	-	-

[*] Costs of 4 PZQ-tablet, dose for adult
[**] *(Number of the health care facility referred to)*
[***] Number of patients diagnosed by the health care facility in 1998 (**bold**: exact numbers; normal: estimated numbers)
[#] Costs of consultation ticket + costs of diagnosis (if performed) + costs of PZQ for adult + costs of transport if the patient is referred
[a] Direct treatment
[b] Unknown to which health post referred
- Not applicable, no *S. haematobium* or *S. mansoni* in area
~ missing value

9

Measuring schistosomiasis case management of the health services in Ghana and Mali

Van der Werf, M. J., De Vlas, S. J., Landouré, A., Bosompem, K. M. and Habbema, J. D. F. Measuring schistosomiasis case management of the health services in Ghana and Mali. Submitted

Abstract

WHO recommends passive case detection by regular health services as a minimum strategy for schistosomiasis morbidity control. To evaluate preparedness of the health systems in Ghana and Mali, we presented four clinical scenarios, two about *Schistosoma haematobium* and two about *S. mansoni*, to health workers. We requested them for an initial diagnosis and case management strategy without informing them about our interest in schistosomiasis. The information was used to determine the chance that a person reporting with schistosomiasis related symptoms would receive praziquantel.

All selected health workers participated. Their initial diagnosis was frequently urinary schistosomiasis for both *S. haematobium* scenarios. For the two *S. mansoni* scenarios, only few mentioned intestinal schistosomiasis. At health centre level, case management in Mali mainly consisted of direct prescription of medication, whereas in Ghana health workers often referred to a hospital or requested a diagnostic test. The ultimate probability of prescribing praziquantel was relatively high for the scenarios with symptoms related to *S. haematobium*, 60% in Ghana and 75 % in Mali, and low for both *S. mansoni* scenarios (<20%). Of the health care facilities that would prescribe praziquantel, 60% (Ghana) and 80% (Mali) had it in stock.

In conclusion, the clinical scenario study showed that patients reporting with *S. haematobium* symptoms can expect proper treatment at approximately half of the health care facilities, whereas those presenting with *S. mansoni* symptoms have only a very limited chance. Considering these facts, it is questionable if passive case detection is a sufficient basis for effective schistosomiasis morbidity control, especially for *S. mansoni* infection.

Introduction

Schistosomiasis is one of the parasitic infections with a serious impact on public health in Africa. It was estimated that the urinary type (*Schistosoma haematobium*) causes haematuria in 70 million and major bladder wall pathology in 18 million individuals in sub-Saharan Africa (Van der Werf *et al.*, in press-b). *S. mansoni*, the intestinal type, is responsible for blood in stool in 4.4 million individuals, and 8.5 million were estimated to have hepatomegaly due to the infection (Van der Werf *et al.*, in press-b). Since the introduction of the effective and safe single dose drug praziquantel (Seubert *et al.*, 1977), WHO has advocated morbidity control (WHO, 1985). The initial strategy was community wide disease specific treatment campaigns with active diagnosis and treatment (vertical approach). In 1991, the emphasis shifted to a more horizontal approach, i.e. control integrated in the Primary Health Care services infection (WHO, 1993).

An essential component of the integrated approach is clinical care for patients that visit health care facilities with complaints related to infection with schistosomes (passive case detection) (Engels *et al.*, 2002). The WHO recommendations for integrated case management requires health workers to diagnose patients by recognising the main symptoms of infection (WHO, 1993). Identified patients should receive prescriptions for praziquantel, and the drug must be available. Also, the use of sensitive diagnostic tests in health care facilities with laboratory facilities is advocated, especially for patients with dysenteric symptoms, as the differential diagnosis is extensive. Studies in Ghana, Mali and Senegal have demonstrated that there is a considerable difference in complying with these recommendations (Van der Werf *et al.*, in press-a, Van der Werf *et al.*, 2002b) (Landouré, personal communication). However, even if prerequisites for case management are met, i.e. health workers have adequate knowledge of the symptoms that may raise suspicion of the disease, are acquainted with treatment options and the prescribed drugs are available, it does not necessarily mean that patients presenting symptoms compatible with schistosomiasis will receive treatment for the infection. They may, for instance, not be suspected of schistosome infection because the presenting symptoms could be due to other diseases. For example, patients presenting with bloody diarrhoea can also receive diagnoses of other infections common in developing countries, such as amoebiasis, trichuris or bacterial infection (Manson-Bahr and Bell, 1987). Therefore, we studied schistosomiasis case management to identify bottlenecks in the process and opportunities for improvement.

Insight into the case management process can be obtained by observation of health care provider-patient contacts which has been done for diseases such as sexual transmitted diseases (Voeten *et al.*, 2001), childhood diarrhoea (Nizami *et al.*, 1996, Cutts *et al.*, 1988) and malaria (Font *et al.*, 2001). However, apart from being time-consuming and expensive, this method is also prone to bias due to changes in behaviour of health workers in the presence of observers (Béria *et al.*, 1998, Beullens *et al.*, 1997). Use of simulated or standardised patients does not have this disadvantage, but it requires extensive training of

volunteers in simulating diseases (Woodward *et al.*, 1985, Rethans and van Boven, 1987). Moreover, we were advised not to use the latter method because doctors would consider it intrusive and offensive and merely a test of their competence. We therefore presented to health workers hypothetical clinical scenarios of patients with symptoms possibly related to urinary or intestinal schistosomiasis. For four scenarios, we assessed the initial diagnosis and the case management process (direct treatment, request of a diagnostic test or referral to another health care facility). The outcomes were used to determine the chance of receiving praziquantel in case such clinical scenarios would present at a health care facility. This approach was applied for the health systems in Ghana and Mali, two countries with a different historical organisation of the health system and a different history of schistosomiasis control..

Methods

Schistosomiasis in Ghana and Mali

Ghana and Mali are West African countries with a medium sized population: Ghana 20 and Mali 11 million inhabitants. Ghana gained independence from Great Britain in 1957 and is now a member of the Commonwealth. Mali is part of francophone West Africa and became independent in 1960. Schistosomiasis (urinary and intestinal) is known to be endemic in both countries. In Ghana, areas with high prevalences of schistosomiasis exist in the north, south and around lake Volta (Lyons, 1974, Scott *et al.*, 1982, Wen and Chu, 1984, Mott *et al.*, 1985a, Ofori-Adjei *et al.*, 1986, Klumpp and Webbe, 1987, Zijlmans *et al.*, 1989, Amankwa *et al.*, 1994, Bosompem *et al.*, 1996, Wagatsuma *et al.*, 1999). In Mali, high prevalence areas are located in Office du Niger, Pays Dogon and Baguineda, an irrigated area near the capital Bamako (Traoré, 1989, Werler, 1989, De Clercq *et al.*, 1994, Kardorff *et al.*, 1994, Dabo *et al.*, 1995a, Traoré *et al.*, 1998a).

In Ghana, a schistosomiasis control programme which delivered praziquantel mass treatment in affected villages was started after the completion of the Akosombo dam in the Volta Region in 1964 (Paperna, 1968, Paperna, 1969). In other parts of the country no official control programmes exist. In Mali, control efforts started in 1982 with the establishment of a national schistosomiasis control programme (Brinkmann *et al.*, 1988). After 1987, activities were decentralised to the district and regional health teams and schistosomiasis control was integrated in primary health care (Traoré, 1996).

Health systems

In Ghana and Mali, governmental health services are based on principles of primary health care and the Bamako Initiative (WHO, 1978, Garner, 1989, Biritwum, 1994). In both countries, health services are organised in district health systems. Each district contains a district hospital, a number of health centres and sometimes one or more private clinics or mission clinics. In the primary health care concept, patients should first contact the health centres (initial level), however, part of the patients will directly visit the district or regional

hospital. Health centres are staffed and equipped to provide basic primary care and preventive services to the population in their coverage area. Patients who cannot be handled at the health centre are referred to the next level, i.e. the district hospitals. These provide curative care to patients who can not be treated as outpatients or who require techniques not available at the primary level. If necessary, health workers in district hospitals refer complicated cases to the regional hospitals. Normally, laboratory diagnosis can be performed at district, regional and mission hospitals. All non-private health care facilities have a pharmacy, which sells a limited number of drugs depending on the level of the health care facility. Although praziquantel is not on the essential drug list in Ghana, it is expected to be available at all levels of the health system. In Mali, praziquantel is on the essential drug list and should therefore be available at all times in adequate amounts and in the appropriate dosage forms, at a price that individuals and the community can afford (http://www.who.int/medicines/organization/par/edl/infedlmain.shtml, accessed on 7-10-2002).

Interviews and data collection

The surveyed areas in Ghana were the North (districts of Kasena/Nankana, Builsa and West Mamprusi), East (North Tongu and South Tongu), Centre (Bosomtwi Kwanwoma and Atwima), and South (Kraboa Coaltar). In Mali, we included Koulikoro region (districts of Kolokani and Banamba), Ségou region (Niono), Mopti region (Bandiagara) and Sikasso region (Kolondiéba). The districts represent different schistosomiasis endemicity levels to cover the overall situation of schistosomiasis control in the country. In Ghana, we selected 10 health care facilities per district, or all health care facilities if there were eleven or less present, i.e. the district hospital, one mission hospital and one private clinic (if present) and a random sample of health centres and mission clinics. In Mali, the district hospital, and randomly, 1 private clinic (if present) and 13 or 14 health centres until a total of 15 health care facilities were included per area. In total, 70 health care facilities were surveyed in Ghana and 60 in Mali. They were grouped into first level health care facilities (health centres, mission clinics and private clinics) and hospitals (district hospitals and mission hospitals). In each selected health care facility we interviewed the person in charge. In case this person was not present, the second in command was interviewed. If there was no health worker present at the time of our visit, the health care facility was visited at another day. All selected health care facilities participated in the study.

After a short introduction which did not reveal our special interest in schistosomiasis control, we presented in random order four clinical scenarios with symptoms related to *S. haematobium* (A, distinct symptoms and B, indistinct symptoms) or *S. mansoni* (C, distinct symptoms and D, indistinct symptoms) infection, see Box. We asked the respondents for their case management if a patient with scenario A, B, C or D would present at their health care facility; their initial diagnosis (working diagnosis) and usual action. We especially wanted to find out (1) if a diagnostic test would be requested and which test, (2) if there was referral for a diagnostic test or treatment, (3) to which health care facility patients

would be referred, (4) what the action would be after a test positive for schistosome eggs and after a test with no abnormalities (negative test), and (5) which treatment would be prescribed.

Clinical scenarios:

(A) 10 year old girl with blood in urine

(B) 40 year old man with blood in urine and painful urination

(C) 10 year old boy with abdominal discomfort and bloody diarrhoea

(D) 30 year old woman with diarrhoea and abdominal discomfort

After discussing the clinical scenarios we asked the respondent if *S. haematobium* and *S. mansoni* were endemic in the coverage area of the health care facility. Thereafter, respondents from areas with reported schistosomiasis were interviewed using a structured questionnaire, which included questions about knowledge of symptoms related to schistosomiasis and availability and costs of diagnostic tests and praziquantel. The results of these interviews were published elsewhere (Van der Werf *et al.*, 2002b, Van der Werf *et al.*, in press-a). We used the data about the availability of praziquantel in the health care facility for calculating the probability that a clinical scenario would receive praziquantel.

Analysis

By multivariate logistic regression (SPSS) we assessed whether the frequency of schistosomiasis as initial diagnosis and direct prescription of praziquantel differed between both countries, health care facility level (first level vs. hospital) or reported endemicity. Other replies were statistically compared using the Exact Chi-square test (SAS). A p-value < 0.05 was considered significant.

The probability of receiving a prescription for praziquantel was calculated by considering all situations were prescription of praziquantel is the outcome of the case management process: (1) direct prescription, (2) after a positive diagnostic test, (3) after a negative diagnostic test (after a positive second diagnostic test, after referral, or directly without a second test or referral), and (4) referral of patients to hospitals. Probabilities were calculated for all health care facilities, irrespective of reported presence of infection. This was because *S. haematobium* was reported in most situations (>70%) and health workers were often not aware of the existence of *S. mansoni* in their coverage area (personal communication Drs Bosompem and Danso-Appiah). As not all referred hospitals were included in our study, we used the average case management strategy of all visited hospitals in the country considering (1), (2) and (3) as above. If a diagnostic test was requested, we took into account that not all infected individuals will be found positive for schistosomiasis by the test. From literature studies it was derived that on average 58% (range 12–94%) of patients with haematuria have *S. haematobium* eggs in a urine filtration

test (Warren *et al.*, 1979, Sarda *et al.*, 1985a, Gigase *et al.*, 1988, Adom *et al.*, 1992, Eltoum *et al.*, 1992, Abdel-Wahab *et al.*, 1992a, Serieye *et al.*, 1996, Mafe, 1997, Hammam *et al.*, 2000b, Hammam *et al.*, 2000a, Gabr *et al.*, 2000, Abdel-Wahab *et al.*, 2000b). Health workers from both Ghana and Mali reported use of the urine centrifugation test, which has a comparable sensitivity (Richards *et al.*, 1984). Therefore, we assumed that 50% of the urine diagnostic tests would give positive result for a haematuria case due to *S. haematobium* infection. For the diagnosis of *S. mansoni* eggs in stool all health workers reported use of the direct smear test. The Kato-Katz method detects eggs in on average 68% (range 27 – 96%) of individuals with blood in stool (Ongom *et al.*, 1972, Arap Siongok *et al.*, 1976, Hiatt, 1976, Hiatt and Gebre-Medhin, 1977, Ripert *et al.*, 1982, Guimaraes *et al.*, 1985, De Lima e Costa *et al.*, 1985, Sukwa *et al.*, 1986, Abdel-Wahab *et al.*, 1990, Eltoum *et al.*, 1993, Habib *et al.*, 2000, El-Hawey *et al.*, 2000, Nooman *et al.*, 2000, Abdel-Wahab *et al.*, 2000a, Barakat *et al.*, 2000). As the direct smear test has a lower sensitivity compared to the Kato-Katz method (Katz *et al.*, 1972), we assumed that 50% of the direct smear tests would give positive result for a blood in stool case due to *S. mansoni* infection.

The eventual probability of receiving praziquantel for a patient reporting at a health care facility with symptoms comparable to scenario A, B, C or D was based on the probability of receiving a prescription of praziquantel and the proportion of health care facilities, among those prescribing, that had it in stock. The proportion having praziquantel in stock was weighed according to the probability that a visit would lead to a prescription, so e.g. 50% after a diagnostic test and the average probability for hospitals after referral.

Results

Eighty-three percent (83%) of the surveyed health care facilities in Ghana and 93% in Mali were first level health care facilities. In Mali, 83% of the respondents reported presence of *S. haematobium* infection in their coverage area and 70% in Ghana. *S. mansoni* infection was also more often reported by health workers from Mali (37%) than Ghana (17%). In Ghana, 21% of the health workers could not recall about the existence of *S. mansoni* and were therefore unaware of the presence of *S. mansoni* in their coverage area.

There was a wide variety in the reported initial diagnosis for the four clinical scenarios in both Ghana and Mali, especially for C and D (Table 9.1). For scenario A, health workers almost uniquely mentioned schistosomiasis as initial diagnosis, whereas for B also urinary infection and sexually transmitted disease (STD) were reported. For C and D, less than 15% of the health workers mentioned schistosomiasis as initial diagnosis. In Ghana, 10 and 20 percent of the health workers from first level health care facilities could not mention an initial diagnosis for respectively scenarios C and D. Most of them (respectively 50 and 77%) would prescribe direct treatment with oral rehydration salts (ORS), antibiotics or metronidazole (data not shown). There was no significant difference in the frequency of schistosomiasis as initial diagnosis between Ghana and Mali and between different health care facility levels. Only for scenario B in Mali, schistosomiasis was more often reported as initial diagnosis in areas endemic for *S. haematobium*. Approximately one

Table 9.1: Initial diagnosis for four clinical scenarios with symptoms related to *S. haematobium* (A and B) and *S. mansoni* infection (C and D), as reported by health workers from Ghana (n=70) and Mali (n=60). See Box for description of clinical scenarios. Values are percentages.

A			B		
Diagnosis	Ghana	Mali	Diagnosis	Ghana	Mali
Schistosomiasis	91	92	Schistosomiasis	57	57
Urinary infection	4	7	Urinary infection	29	18
Trauma	0	2	STD	10	18
Diabetes	1	0	Prostatitis	0	2
Black water fever	1	0	Renal infection	0	2
Unknown	1	0	Neoplasm	0	2
			Enlarged prostate	1	0
			Unknown	3	2

quarter of the health workers also mentioned a second possible diagnosis. The diversity of second diagnoses was comparable to the first initial diagnosis, only urinary bacterial infection was more often mentioned as second diagnosis for scenarios A and B.

About 7% of the health centres in Ghana and 5% in Mali would request a diagnostic test, irrespective of the clinical scenario presented (Figure 9.1). In fact, all health care facilities with laboratory facilities in Ghana (20% of the surveyed health care facilities) and all but one in Mali (8%), would request a diagnostic test for two or more of the clinical scenarios (not shown). All laboratories used the urine centrifugation test for the diagnosis of *S. haematobium* infection and simple direct smear test for the diagnosis of *S. mansoni* infection. In Ghana, about 60% of the health workers in health centres reported to refer clinical

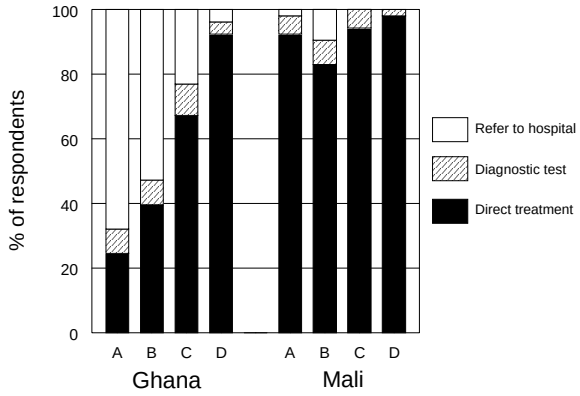

Figure 9.1: Reported case management by health workers in health centre in Ghana (n = 53) and Mali (n = 53) for four clinical scenarios with symptoms related to *S. haematobium* (A and B) and *S. mansoni* infection (C and D). See Box for description of clinical scenarios. The drugs prescribed in case of 'direct treatment' are given in Table 9.2.

Table 9.1 (continued)

C			D		
Diagnosis	Ghana	Mali	Diagnosis	Ghana	Mali
Bacterial infection	44	25	Food poisoning	14	37
Amoebiasis	14	32	Parasitic infection	20	28
Parasitic infection	21	22	Bacterial infection	17	13
Schistosomiasis	3	15	Malaria	19	5
Malaria	4	2	Viral infection	9	2
Food poisoning	0	5	Amoebiasis	1	10
Lack of water/food	1	0	Schistosomiasis	0	2
Viral infection	1	0	Vaginal infection	0	2
Unknown	10	0	Cholera	0	2
			HIV infection	1	0
			Unknown	19	0

scenario A and B, mainly because they believed that they were not allowed to treat *S. haematobium* cases themselves.

Almost all health workers in health centres in Mali would prescribe direct treatment for the four presented clinical scenarios (Figure 9.1). In Ghana, less health workers performed direct treatment, especially for scenario A and B (respectively 25 and 40%). In both countries, the *S. haematobium* scenarios would more often receive a prescription for praziquantel than the *S. mansoni* scenarios (Table 9.2). Furthermore, Malian health workers would more frequently prescribe praziquantel than Ghanaian health workers for all four clinical scenarios ($p < 0.05$). Seventy-five percent (75%) of the health workers in Ghana that mentioned urinary schistosomiasis as initial diagnosis for scenario A and B and 98% in Mali would prescribe praziquantel alone or in combination with other drugs (in particular antibiotics) if the patient was not referred. Approximately 30% of the health workers in Ghana would prescribe a combination of three drugs, in Mali this was 15-20%.

Figure 9.2 shows the probability that patients comparable to the clinical scenarios would receive a prescription for praziquantel, accounting for referral and assuming 50% positive after diagnostic testing. In both countries, scenarios A and B had a much higher chance of receiving a prescription for praziquantel (about 60% for Ghana and 75% for Mali) than scenarios C and D (both about 12%). The total probability was comparable between the two countries, but in Ghana most praziquantel prescriptions (especially for scenario A and B) were after referral, whereas this was direct treatment in Mali.

The eventual probability of receiving praziquantel for a patient reporting at a health care facility with symptoms comparable to scenario A, B, C or D is presented in Table 9.3. Within both countries, the availability of praziquantel appears to increase with the decreasing probability of prescription over scenarios. This is mainly because hospitals (which usually have praziquantel in stock) make the largest part of situations where

Table 9.2: Reported direct treatment for four clinical scenarios with symptoms related to *S. haematobium* (A and B) and *S. mansoni* infection (C and D), as reported by health workers from Ghana and Mali. See Box for description of clinical scenarios. Values are percentages.

Treatment	A		B	
	Ghana (n=15)	Mali (n=53)	Ghana (n=23)	Mali (n=47)
Praziquantel	47	83	13	51
Praziquantel + Antibiotics	7	4	4	13
Praziquantel + Other*	0	0	4	0
Antibiotics	20	9	57	32
Antibiotics + Other*	13	2	22	4
Other*	13	2	0	0
Total praziquantel	54	87	21	64

* Other includes: chloroquine, metrifonate, pain treatment, mebendazole, metronidazole, quinton and potassium solution

** Other includes: oral rehydration salts (ORS), pain treatment, chloroquine, antispasmodic, antacids, multivitamins, immodium, kaolin suspension, salt infusion and sulfaterazol

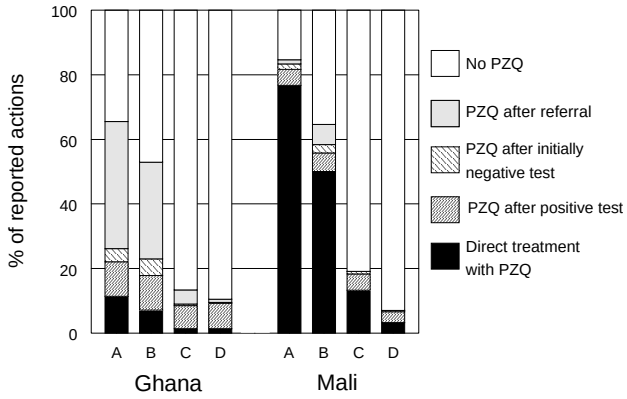

Figure 9.2: Percentage (%) of reported actions ending in prescription of praziquantel (PZQ) by health workers in the Ghanaian (n = 70) and Malian (n = 60) health system for four clinical scenarios. The category 'No PZQ' comprises all situations where PZQ was not prescribed: prescription of other drugs related to a different initial diagnosis or diagnostic test, with or without referral to hospital. [1]

praziquantel is less often prescribed. Overall, praziquantel was more available in Mali than in Ghana. The average availability of the drug in each health system will be lower than the values in Table 9.3, as presence of the drug will lead to prescription, or vice versa. For

[1] One Ghanaian health worker had never seen a patient like scenario C and could therefore not answer the questions. In Mali, one health worker reported for scenario D to wait for two days if the symptoms would disappear.

Table 9.2 (continued)

Treatment	C		D	
	Ghana (n=41)	Mali (n=54)	Ghana (n=55)	Mali (n=54)
Praziquantel	0	6	0	0
Praziquantel + Antibiotics	0	2	0	0
Praziquantel + Metronidazole	0	4	0	4
Praziquantel + Antibiotics + Metronidazole	2	4	2	0
Antibiotics	12	7	4	0
Metronidazole	22	30	5	17
Antibiotics + Metronidazole	10	24	0	15
Antibiotics + Metronidazole + Other**	10	6	0	17
Metronidazole + Other**	12	15	14	20
Antibiotics + Other**	20	4	9	13
Other**	12	0	65	15
Total praziquantel	2	16	2	4

example, for scenarios C in Ghana, 3 out of 5 hospitals that prescribed praziquantel had it in stock, while this was 1 out of 5 of those which did not prescribe.

In agreement with the probability of prescription, the eventual probability of receiving praziquantel is higher for clinical scenario A and B (respectively 30 and 60%) than for C and D (both 10%).

Table 9.3: The probability of receiving praziquantel (PZQ) for patients comparable to clinical scenarios A, B, C or D, based on the probability of receiving a prescription of PZQ (from Figure 9.2) and the proportion of health care facilities among those prescribing that had it in stock.

Clinical scenario	Ghana			Mali		
	PZQ prescribed (%)	PZQ in stock (%)	Receiving PZQ (%)	PZQ prescribed (%)	PZQ in stock (%)	Receiving PZQ (%)
A	66	47	32	85	72	61
B	53	56	30	65	83	54
C	13	74	10	19	74	14
D	11	92	10	7	88	6

Discussion

All selected health workers agreed to participate in our study, suggesting that our research methodology was highly acceptable. We also had a strong impression that the respondents enjoyed answering the questions; especially health workers from first level health care facilities were pleased about our interest in their daily work. It was feasible to present the clinical scenarios to all professional levels, including health workers with limited training. We consider these important observations because co-operation of health workers is essential to come to reliable answers. In hospitals, there were more health workers performing case management than doctors only. Initially, we interviewed different health

workers (of different professional levels) in hospitals to gain insight into case management of hospitals. However, when interviewing several persons in one health care facility it was difficult to keep the subject of the research project hidden for the next respondents, with a risk of unreliable answers. Therefore, we only presented the results from the interview with the first person, which was the one in charge of the health care facility or his/her representative.

Our experiences with the research methodology were more positive than those of researchers that used other methods for studying case management. Studies using simulated patients reported high refusal to participate (8 to 32% of the selected group) because, contrary to our experiences with the clinical scenarios, the method was not appreciated by the respondents (Rethans and van Boven, 1987, Russell *et al.*, 1991, Bowman *et al.*, 1992, Tamblyn *et al.*, 1992). Also, a number of participants (4 to 26%) unmasked the simulated patient (Woodward *et al.*, 1985, Rethans and van Boven, 1987, Russell *et al.*, 1991, Tamblyn *et al.*, 1992). In general, quality of health worker performance is often less favourable (i.e. compared to standards) if measured by simulated patients or observation studies compared to questionnaire surveys or clinical scenarios (Rethans and van Boven, 1987, Russell *et al.*, 1991, Kopelow *et al.*, 1992, Nizami *et al.*, 1995, Ofori-Adjei and Arhinful, 1996, Voeten *et al.*, 2001). This can be explained by the fact that health workers probably give socially desirable answers in questionnaire surveys. We believe that in our study there was no reason nor pressure for this, because the subject of our mission (schistosomiasis case management) was only revealed after the clinical scenarios were presented. To test the validity of the clinical scenario method, it would be interesting to compare it to observations of health provider-patient contacts or to the results of simulated patients.

Figure 9.2 shows that both patients with distinct and indistinct symptoms of schistosome infection have a rather limited prospect for prescription of praziquantel if they report with symptoms at a health care facility, especially cases due to *S. mansoni* infection (scenarios C and D). It should be noted that limited prescription of praziquantel does not necessarily indicate low quality of case management, as the scenarios might very well represent patients with other diseases. Especially symptoms of *S. mansoni* infection are non-specific (Gryseels, 1992, Guyatt *et al.*, 1995). Therefore, depending on the epidemiological situation in the coverage area of the health care facility, it could in fact be the best clinical practice to treat these scenarios as other diseases, e.g. amoebiasis. As haematuria is a more specific symptom and a well-known indicator of *S. haematobium* infection (Van der Werf *et al.*, in press-a)(Landouré, unpublished results), alternative diagnoses were not often mentioned and praziquantel was often (directly) prescribed. If direct treatment was the initial action, praziquantel would significantly more often be directly prescribed for clinical scenarios A and B by health care facilities in areas reported endemic for *S. haematobium*. This could not be tested for clinical scenarios C and D as only very few health workers prescribed praziquantel directly. The quality of the management of the clinical scenarios could be assessed by relating the answers from the respondents to case management guidelines or

to the judgement of experts. For example, by means of the Delphi method experts can come to a group consensus on which reported case management policies were adequate for the clinical scenarios, given a reasonable knowledge about the epidemiological situation of different diseases which may cause the presented scenarios (Milholland *et al.*, 1973).

The probability of receiving a prescription for praziquantel as presented in Figure 9.2 is the most favourable in the sense that it can only be obtained if all patients comply with referral and buy the prescribed medication. Most likely, not all patients will comply with referral (and visit another health care facility for diagnosis or treatment) due to time and money constraints. Also, not all patients that receive a prescription for praziquantel will be able to buy the drug, as it is still relatively expensive (about 1 Euro for the normal dose of 4 tablets for adults) and not always available in the health care facilities where it is prescribed.

It follows from our study that patients with symptoms similar to scenarios A, B, C and D that are due to schistosome infection have a low probability of adequate treatment. For scenarios C and D, the low rate of prescription (mainly due to low alertness for *S. mansoni*, see above) is the limiting factor. For scenarios A and B, both prescription and availability of the drug limit the probability of receiving praziquantel. It is a subject of further study to find out whether this probability can best be improved by changing the procedures of the health systems (by training of health workers in identifying schistosomiasis patients or changing algorithms) or making praziquantel available at larger scale. Higher availability may increase the number of prescriptions, and higher awareness of schistosomiasis may increase procurement of praziquantel. As said above, especially for scenarios C and D, changing the procedures does not necessarily result in the best strategy, as other causes than *S. mansoni* may be more likely explanations of the symptoms. In endemic areas, it is always recommendable to have some praziquantel available in the health system.

In conclusion, the use of clinical scenarios is a valuable additional research method for the assessment of schistosomiasis case management and provides a quantitative description of the process of diagnosis and treatment. It is a simple fast method and it is well accepted by health workers at different levels of the health care system. If the presented clinical scenarios with distinct and less distinct symptoms were really due to schistosome infection, most health care facilities in Mali (60%) and about 30% in Ghana would (eventually) prescribe praziquantel for *S. haematobium* patients and also have it in stock. *S. mansoni* patients would only rarely receive a prescription for praziquantel (<15%). Moreover, only a minority of the individuals with symptoms caused by *S. haematobium* or *S. mansoni* infection (respectively haematuria and blood in stool) will visit the regular health services for treatment (15%), Danso-Appiah (unpublished results). Therefore, passive case detection is probably only an effective method for morbidity control in areas with very high endemicity of schistosome infection where most cases with haematuria or bloody diarrhoea are due to schistosome infection. In these situations health workers can be trained in prescribing praziquantel and the population sensitised to seek health care (e.g. outbreak area in Northern Senegal). Otherwise additional measures might be necessary.

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10

General discussion

10.1 The Global Burden of schistosomiasis

In Part I of this thesis, we presented a new method to estimate the number of individuals with morbidity due to schistosome infection. We first assessed the association between prevalence of schistosome infection and prevalence of pathology or morbidity from all available published studies. Thereafter, the number of individuals with symptoms due to infection with schistosomes were estimated using data on the prevalence of schistosome infection and taking into account heterogeneity in infection levels of populations within countries. In the following paragraphs, we discuss our choices and the consequences. We also attempt to re-calculate the burden of schistosomiasis in DALYs (Disability Adjusted Life Years, sum of years of life lost and years of life lived with disability).

10.1.1 The association between prevalence of infection and morbidity

The association between prevalence of *S. haematobium* infection and morbidity in schools or communities is usually assumed to be linear (straight line) (Jemaneh *et al.*, 1993, Lwambo *et al.*, 1997a, Lengeler *et al.*, 1991, Amali, 1994, Chippaux *et al.*, 2001). For estimating the number of individuals affected by schistosomiasis, we consider the straight line determined by linear regression less suitable, because it is not biologically realistic and it easily results in under- or overestimation. Also, it does not preclude invalid prevalences of morbidity, e.g. below 0% in uninfected populations or above 100% in populations with 100% prevalence of infection. Therefore, in our studies we derived a non linear equation, which included that morbidity mainly develops in individuals with high intensities of infection, so that prevalence of morbidity should rise faster than prevalence of infection. Furthermore, we took into account that also in populations non-endemic for schistosome infection, morbidity such as that found in schistosomiasis patients can be detected in a percentage. This baseline prevalence of morbidity was not included in our calculations of the estimated number of individuals with morbidity due to schistosome infection. We assumed that the baseline prevalence of morbidity (parameter *a* in the equation), which largely depends on populations uninfected with schistosomiasis or with low endemicity, is equal for low and highly endemic populations. It is likely that this is an oversimplification as infectious diseases tend to cluster (Booth *et al.*, 1998a), which would result in an increasing baseline prevalence of morbidity. Schistosome infected individuals have probably also been exposed to other agents, e.g. in environments were no sanitary facilities are available, the risk of transmission of schistosomiasis is increased but at the same time of amoebiasis (both responsible for bloody diarrhoea). Also, individuals living in rural areas are more likely to be poor and might have nutritional deficiencies, making them more susceptible for any disease. We believe that our assumption of a horizontal baseline is not seriously jeopardised by clustering of diseases as the baseline is probably mainly determined by misclassification, which is not associated with the prevalence of schistosome infection. In the most likely situation, i.e. a slightly increasing baseline with increasing prevalence of infection, estimates of the number of individuals with morbidity are somewhat smaller than those presented by us in Tables 5.2 and 5.3. Disentangling

morbidity caused by schistosome infection and by other diseases is difficult. One laborious method is to detect all diseases that can cause a certain symptom in a population, e.g. bloody diarrhoea can be due to intestinal schistosomiasis and among other things amoebiasis, shigella and campylobacter infection (Manson-Bahr and Bell, 1987), and treat each disease separately. The amount of morbidity that resolves after each treatment can than be attributed to the disease. A complication is that some drugs are active against several diseases.

To illustrate the difference between a linear and a non-linear equation we calculated the estimated prevalence of bladder pathology in a community with 5% prevalence of *S. haematobium* infection and with 50% prevalence. In a community with 5% prevalence of infection, using a linear regression equation ($y = 0.042 + 0.79x$, SPSS PC) results in a much higher estimated prevalence of bladder pathology (i.e. 3.9%) than using our non-linear equation (Chapter 5), i.e. 1.7%. The linear equation results in a lower estimate of bladder pathology in communities with 50% prevalence of infection than our equation (i.e. 39% vs. 44%). As most countries have a prevalence of *S. haematobium* infection around 20%, the use of a linear equation would usually overestimate the number of individuals with morbidity (Table 10.1). Using our example, the linear equation estimated that 105 million individuals would have bladder pathology due to *S. haematobium* infection in Africa, whereas the non-linear equation estimated 88 million.

10.1.2 Morbidity estimates

The estimated number of individuals with morbidity (Chapter 5) should be interpreted taking into account uncertainty in the original data obtained from the literature, in the estimated equations, in the prevalence of infection data used for the calculations and in the degree of heterogeneity of population prevalences within endemic areas (Table 10.1).

Table 10.1: Effect of alternative assumptions for the calculation of morbidity estimates for schistosome infection: ↓ indicates reduction and ↑ increase in the number of individuals with morbidity.

Item	Alternative	Effect on morbidity estimates
Equation	Linear	↑
Baseline	Decreasing with prevalence of infection	↑
	Increasing with prevalence of infection	↓
Estimated prevalence of infection in endemic countries	Lower	↓
	Higher	↑
Heterogeneity	Lower	↓
	Higher	↑
Symptoms*	Unique	↑
	Combined	↓

* For the calculation of the burden of schistosomiasis it is assumed that (1) patients can only have one symptom concurrently (Unique) or (2) severe symptoms are present in those individuals with milder symptoms (Combined).

We have little information about the quality of the data derived from literature. The studies differed largely in size and methods used for measuring infection and morbidity. By only including studies that used direct parasitological diagnostic methods (Kato-Katz, direct smear for *S. mansoni* and urine centrifugation and filtration for *S. haematobium*) we attempted to reduce variance in the estimated prevalences of infection. Furthermore, *S. mansoni* prevalences were standardised to the expected test result of a default diagnostic technique (i.e. single 41.7 mg Kato-Katz faecal sample). Also for the methods measuring morbidity we have defined minimum standards. The resulting uncertainty in the estimated equations due to differences in the quality of the original data is partly reflected in the confidence intervals.

We have used a linear equation (straight line) to assess the impact of recall period length on reported haematuria in Chapter 4 using standard statistical procedures (covariance analysis) and found no impact of recall period length on the association between prevalence of infection and prevalence of haematuria. The data-sets for other morbidity types (dysuria, diarrhoea, blood in stool and abdominal pain) measured by questionnaires using different recall period lengths were insufficient to test the impact of recall period length, but an effect did not seem to be apparent. The prevalence of bladder pathology measured by ultrasound differed clearly between schools and communities with similar prevalence of infection. For the other associations there was no clear indication for an effect of study setting on the association (discussed in Chapter 2 and 3). Differences in the occurrence of pathology or morbidity in diverse geographical areas were reported by others for *S. haematobium* (Tanner *et al.*, 1983, Mott *et al.*, 1985b) and *S. mansoni* (Gryseels, 1989). Our data sets did not suggest such differences.

The mean prevalence of infection in endemic areas in a country was estimated using information from schistosomiasis survey data (published and unpublished sources). Often prevalence of infection for pre-school children and adults was estimated from data on school children only (Guyatt *et al.*, 1999b, Brooker *et al.*, 2000b, Brooker *et al.*, 2002). It has been shown before that prediction of community prevalence of infection from data of schoolchildren is prone to bias (Brooker *et al.*, 2000a). Also, the number of administrative units in Africa for which there were data was only 30% (range 0 to 100% for different countries) requiring extrapolation and modelling for the areas where no data were available by using models of the distribution of infection in relation to environmental variables (Brooker *et al.*, 2000b). Although the quality of the prevalence of infection data can be disputed, at present this is the best available. Furthermore, the data were verified by counterchecking with other information (Doumenge *et al.*, 1987) and expert opinion.

The overall prevalence of infection in endemic areas in a country usually does not accurately reflect the local situation as some areas will have a high prevalences of infection due to, for example, the presence of an irrigation scheme, whereas others will hardly have infected cases (especially semi-urban areas). In our calculations, heterogeneity in infection prevalences (standard deviation = 0.6) was especially important for symptoms that are strongly non-linearly related to prevalence of infection (e.g. diarrhoea and blood in stool

due to *S. mansoni* infection (Figure 2.2) and bladder wall pathology and haematuria due to *S. haematobium* infection (Figure 3.1)). If we had not taken into account heterogeneity, morbidity estimates would have been much smaller (for bladder pathology 23 million instead of 88 million), whereas stronger heterogeneity would result in higher estimates (i.e. standard deviation 0.8 results in 130 million cases of bladder pathology). For estimating the heterogeneity of infection, we only had limited data-sets available, i.e. two studies from Tanzania for *S. haematobium* (Lengeler *et al.*, 1991, Guyatt *et al.*, 1999a) and four studies in Burundi (Gryseels and Nkulikyinka, 1988), Congo (Lengeler *et al.*, 2000), Côte d'Ivoire (Utzinger *et al.*, 2000) and Egypt (Barakat *et al.*, 1995) for *S. mansoni*. Especially for *S. haematobium*, availability of more data from other countries might improve the estimate of heterogeneity. Also, the included studies provided data for one district and not for all districts in an endemic region and it is likely that the degree of heterogeneity in all districts in endemic regions is somewhat higher. Furthermore, it is possible that heterogeneity differs between countries, e.g. low heterogeneity when the disease is omnipresent and high when only occurring in small irrigation areas. Improved morbidity estimates could be obtained by (1) measuring heterogeneity from data on prevalence of infection in communities distributed over countries and from different countries, (2) by calculating morbidity estimates for districts using prevalence of infection data from districts or (3) combination of (1) and (2). Both solutions require additional data, which can only come from extensive research or control programs.

10.1.3 Mortality

Premature death attributes significantly to the Global Burden of a Disease. However, the number of studies providing information about mortality due to schistosomiasis is limited and insufficient for estimating overall mortality due to schistosome infection (Katz, 1998, Kheir *et al.*, 1999). Therefore, we calculated schistosomiasis mortality from the estimated number of cases with two types of life-threatening morbidity, i.e. non functioning kidney for *S. haematobium* and haematemesis for *S. mansoni* infection (Chapter 5). The estimated number of deaths due to these causes (280,000 per year) is substantially higher than the 4,000 death that were attributed to schistosomiasis and used for the first Global Burden of schistosomiasis calculations (Murray and Lopez, 1996). We realise that our estimates were based on limited data available, and researchers and policy makers should be cautious with uncritically referring to them as done by Pearce et al., 2002. However, we are convinced that the number of deaths due to schistosomiasis is a multiple of 4,000. Also because other causes of death have not even been included, e.g. Katayama syndrome, ectopic lesions, bladder cancer and liver failure. It must be kept in mind that the acquired immunodeficiency syndrome (AIDS) has become an important competitive cause of death, especially in East Africa. Direct information on mortality requires large numbers of individuals to be studied, necessitating establishment or improvement of vital health statistics data collection in developing countries.

10.1.4 Scarce data

For a considerable number of less frequently occurring symptoms (cercarial dermatitis, Katayama fever, non functioning kidney, bladder cancer, ectopic morbidity) and for death due to schistosomiasis (see *10.1.3*), information from field studies was not or insufficiently available for estimating an association with prevalence of infection. Alternative methods could perhaps be used in these cases.

As an example, we show a method for estimating mortality from bladder cancer due to *S. haematobium* infection. No direct information was available, so we had to use information about the mortality rate for all types of bladder cancer and the prevalence of *S. haematobium* infection. In Egypt, the bladder cancer age-standardised mortality was 10.8 per 100,000 per year for men and 2.3 per 100,000 per year for women in the 1950s in Egypt (La Vecchia *et al.*, 1993) and the prevalence of *S. haematobium* was 25.8% in the Nile delta area in 1962 (Farooq *et al.*, 1966). As active control measures (mass treatment campaigns with praziquantel) have only been introduced after 1980, we assume that the prevalence of infection in the 1950s was comparable to that in 1962. It is likely that there is an underestimation of the number of bladder cancer deaths because probably not all cancer deaths were registered in the 1950s due to lack of medical facilities for diagnosis and incomplete registration. Assuming 50% of the bladder cancer deaths being registered correctly, this results in a mortality rate of 21.6 per 100,000 per year for men and 4.6 per 100,000 per year for women. From literature we derived that *S. haematobium* infection only causes squamous cell type carcinoma (Mostafa *et al.*, 1999). We assumed that in Egypt all bladder cancers of this type were caused by *S. haematobium* infection. Furthermore, we used the figure of the general death rate of bladder cancer and supposed that the death rate due to bladder cancer of the squamous cell type was similar. A study from 1961 (Hashem, 1961) reported that in Egypt 62.3% of all bladder cancers were of squamous cell type. This means that the number of death due to squamous cell type bladder tumours in Egypt was 13.5 per 100,000 per year for men and 2.87 per 100,000 per year for women. It is reasonable to assume that bladder cancer only occurs in individuals with severe infection (on average > 50 eggs/10 ml). Using an existing stochastic egg count model (described in Chapter 2 and adjusted to S. haematobium, De Vlas personal communication) we calculated that a prevalence of *S. haematobium* of 25.8% corresponds to 16.4% with severe infection. This means that a fraction of 0.000823 of the severely infected men and 0.000175 of the severely infected women will die of bladder cancer due to *S. haematobium* infection each year. As half of the population is male and the other half female, we used the average fraction of severely infected men and women that will die of bladder cancer each year. This results in about 13,000 deaths due to squamous cell bladder carcinoma caused by *S. haematobium* infection in Africa as a whole after applying heterogeneity in prevalences of (severe) infection between communities. Again, this figure should be used cautiously and particularly be considered as an illustration, because they were based on limited data and numerous assumptions.

10.1.5 Disability weights

In the first Global Burden of Disease Initiative, severity of disease was assessed using the person-trade-off method (Murray and Lopez, 1997b): Severity of twenty-two indicator disorders was judged by a group of health professionals from each region of the world, which produced 7 disability classes (Murray and Lopez, 1996). Thereafter, all disabling sequelae included in the Global Burden of Disease calculations were rated across these seven disability classes and the average disability weight was calculated. Disability weights range from 0.0 corresponding to perfect health and 1.0 to death. For schistosomiasis, infection was ranked in these classes and a low disability weight calculated (i.e. 0.005 for children and 0.006 for adults carrying the infection). Differences between *S. haematobium* and *S. mansoni* infection were not accounted for. As our studies showed that *S. haematobium* infection has a much stronger association with morbidity this was not a correct assumption.

In our attempt to come to new DALY estimates, we used the lowest disability classes 1, 2 and 3 for determining the disability weights of several symptoms caused by schistosome infection: Class 1 has indicator conditions vitiligo on the face and weight for height less than 2 SDs (disability weights 0.00 – 0.02); Class 2 watery diarrhoea, severe sore throat and severe anaemia (disability weights 0.02 – 0.12); and Class 3 radius fracture in a stiff cast, infertility, erectile dysfunction, rheumatoid arthritis and angina (disability weights 0.12 – 0.24). Each symptom was assigned to a disability class and the mean disability weights of the classes were allocated, respectively 0.01, 0.07 and 0.18 see Table 10.2.

More exact calculations of the DALYs lost due to schistosomiasis morbidity would come from applying disability weights determined for each specific symptom caused by schistosome infection. These can be obtained by using the methods described in the Global Burden of Disease literature or by using modified methods (Murray and Lopez, 1996, Essink-Bot *et al.*, 2002, Baltussen *et al.*, 2002). It also requires information of the clustering of symptoms in individuals, which can be obtained from field studies collecting information of occurrence of several symptoms on the individual level, which are hardly available.

It has been debated if health status preferences (reflected by disability weights) should be allocated by health workers such as done in by the Global Burden of Disease Initiative or by lay people (Baltussen *et al.*, 2002, Jelsma *et al.*, 2000). The former have a better understanding of a wide range of health states, but the issues at stake refer to the allocation of societal resources, making lay people more suitable. Also the universal applicability of disability weights is not accepted by all researchers (Ustun *et al.*, 1999). We think that it might be practical to use the Global Burden of Disease weights for international comparison. However, for priority setting and resource allocation the opinions of the local population should be taken into account. As for the question if these should be experts or lay people, opinions differ (Williams, 1999). It is interesting to know that Baltussun *et al.* (2002) showed that preferences of local health professionals may very well be used as a proxy for lay people's preferences.

10.1.6 Morbidity due to schistosomiasis

In this section we attempt to calculate DALYs lost due to schistosomiasis morbidity and mortality using our estimates of the number of individuals with schistosomiasis morbidity and the disability classes of the Global Burden of Disease Initiative (Murray and Lopez, 1997b). Thereafter, we compare these to the earlier estimates without discounting and age weighing. As the original assumptions and methods used for calculating the Global Burden of schistosomiasis were not clearly stated in the underlying publications, it was not possible to exactly reproduce them using the new morbidity estimates (Murray and Lopez, 1996).

In our calculations, we have estimated the number of individuals with each symptom separately. Evidently, some individuals, especially those with (a history of) high worm loads, have more than one symptom concurrently. Thus, the total number of individuals suffering from symptoms due to infection with schistosomes cannot be derived from simply summing up our estimations. For the DALY calculations, we used the conservative assumption that all severe symptoms are present in those individuals with milder symptoms (i.e. No. affected in Table 10.2). For example, all individuals with moderate or major hydronephrosis are among the group with dysuria, so the number of individuals with dysuria and no severe symptoms is 13 million (32 – 9.3 – 9.6 million). Of the 70 million individuals with haematuria, 32 million will also have dysuria, thus 38 million are counted with only haematuria. Our estimations for diarrhoea and blood in stool were lower than those for hepatomegaly and splenomegaly. Following the same reasoning, there were no individuals with only diarrhoea or blood in stool due to *S. mansoni* infection.

Table 10.2: Estimated DALYs (Disability Adjusted Life Years) lost by symptom due to infection with schistosomes in sub-Saharan Africa. It is assumed that severe symptoms are present in those individuals with milder symptoms. Individuals are only counted for the most severe symptoms, presented in No. affected.

Morbidity	Disability class*	Disability weight	No. with symptoms $\times 10^6$	No. affected $\times 10^6$	DALYs $\times 10^6$
S. haematobium					
Haematuria	1	0.01	70	38	0.38
Dysuria	1	0.01	32	13	0.13
Moderate hydronephrosis	2	0.07	9.3	9.3	0.65
Major hydronephrosis	3	0.18	9.6	9.6	1.7
Total DALYs					2.9
S. mansoni					
Diarrhoea	2	0.07	0.78	0.0	0.0
Blood in stool	1	0.01	4.4	0.0	0.0
Hepatomegaly	1	0.01	8.5	2.2	0.022
Splenomegaly	1	0.01	6.3	6.0	0.060
Ascitis	3	0.18	0.29	0.14	0.025
Haematemesis incidence	3	0.18	0.15**	0.15**	0.0021
Total DALYs					0.11

* Disability class 1 has indicator conditions vitiligo on the face and weight for height less than 2 SDs; Class 2 watery diarrhoea, severe sore throat and severe anaemia; and Class 3 radius fracture in a stiff cast, infertility, erectile dysfunction, rheumatoid arthritis and angina

** See Appendix C, Chapter 5, duration of haematemesis is estimated at 4 weeks

The occurrence of several symptoms in one person may cause more suffering than the presence of the most severe symptom only. However, we used the conservative assumption that implied that the most severe symptom determined the disability class.

The preliminary findings presented in Table 10.2 are certainly in accordance with the statement of the joint WHO Expert Committees on the Prevention and Control of Schistosomiasis and Soil-transmitted Helminthiasis that the Global Burden of schistosomiasis is significantly underestimated (WHO, 2002). We show a higher loss of DALYs in sub-Saharan Africa (3.1 million) than reported by the Global Burden of Disease Initiative for the same region (1.1 million DALYs lost in 1990 without discounting and age weighting and 1.3 million with discounting and age weighting) (Murray and Lopez, 1996). Our estimate was even conservative because we assumed that all individuals with severe symptoms were part of the group suffering from milder symptoms and a disability weight was only attributed to the most severe symptom. Also, DALYs lost due to mortality were not included in our calculations. The Global Burden of Disease Initiative estimated 4,000 deaths due to schistosomiasis in sub-Saharan Africa in 1990. Assuming that per death about 20 years of life are lost and applying no discounting nor age-weighting, only 80,000 DALYs of the 1.1 million are lost due to mortality resulting in about 1 million DALYs lost due to morbidity according to the Global Burden of Disease Initiative calculations. Our mortality estimates were considerably higher than those used by the Global Burden of Disease Initiative. If we make a conservative calculation assuming 50,000 deaths due to schistosomiasis (instead of 280,000 + 13,000 mentioned in Chapter 5 and 10.1.4), the DALYs lost due to mortality are 1 million making our total DALYs lost 4.1 million. Finally, we restricted ourselves to consequences of schistosomiasis about which some quantifications could be found in literature. A significant amount of the burden could be due to a reduction in growth, physical fitness or cognitive development (Stephenson, 1993, Nokes and Bundy, 1994, Kvalsvig *et al.*, 1991).

The higher loss of DALYs calculated in this thesis compared to those published by the Global Burden of Disease Initiative for 1990 cannot be explained by an increase in the prevalences of schistosome infection. There is a general agreement that the number of individuals infected with schistosomes has not considerably changed over the last decade (Crompton, 1999, Brooker *et al.*, 2000b, Chitsulo *et al.*, 2000). Schistosomiasis control successes were achieved in several countries such as Morocco and China, but in other countries, such as Senegal, schistosomiasis has expanded due to the construction of dams and irrigation schemes. Also, the number of individuals living in areas endemic for schistosomiasis has risen because of an increasing world population.

If we compare our morbidity estimates to those published by the WHO Expert Committee on the control of schistosomiasis (WHO, 1993), our estimates were somewhat lower. Their crude calculations resulted in 17 million individuals with severe disease (not defined) (10% of the 166 million infected with *S. haematobium* or *S. mansoni* in sub-Saharan Africa) and 82 million with symptoms (55% of those infected without severe disease). We

estimated 10 million individuals with severe disease (major hydronephrosis, ascitis and haematemesis) and 69 million with milder symptoms.

In conclusion, our DALY calculations result in a significantly higher burden of schistosomiasis in Africa than the estimations of the Global Burden of Disease Initiative. However, our number of individuals with schistosomiasis related morbidity was still somewhat lower than the crude estimates of the WHO Expert Committee.

10.1.7 Possibilities for further research on the burden of schistosomiasis

The presented morbidity estimates can be improved upon and updated if new information becomes available. Especially data on severe morbidity (non-functioning kidney, haematemesis and ascitis) and mortality due to schistosomiasis were scarce and insufficient to obtain good estimates. If new studies or registries provide additional data on population level, these can be used for improving our estimates.

We attributed the symptoms of schistosomiasis to disability classes and allocated the average disability weight of the class. For more precise recalculation of the DALYs lost due to schistosomiasis using morbidity estimates instead of infection disability weights should be determined for the individuals symptoms according to the methods described by the Global Burden of Disease Initiative or by using modified methods.

Prevalence of infection data were only available for Africa. As *S. haematobium* and *S. mansoni* infection are also endemic outside Africa (e.g. Brasil and middle east) morbidity estimates need to be calculated for these countries to arrive at a Global Burden of Schistosomiasis. It must be noted that this addition will only slightly increase our estimates as relatively few infected individuals (9 million) are found outside Africa (Chitsulo *et al.*, 2000) even though some have suggested that *S. mansoni* infection causes more severe morbidity in Brazil due to the recent introduction of the infection.

Disease caused by *S. japonicum* infection also contributes somewhat to the Global Burden of schistosomiasis. Approximately 1.5 million individuals are infected with this species and it is supposed to cause more severe symptoms than *S. mansoni* infection (Jordan *et al.*, 1993, Chitsulo *et al.*, 2000). Information on *S. japonicum* prevalence levels and prevalence of morbidity was mainly available from the Chinese literature and therefore not readily accessible. In 2003, a collaborative research project will start with Chinese researchers to explore this literature on infection and morbidity. By using the developed methodology, estimates of morbidity due to *S. japonicum* infection may then be calculated. Two other species, *S. intercalatum* and *S. mekongii*, are only present in a small number of individuals and of minor importance for the Global Burden of schistosomiasis.

It would also be interesting to validate the calculated morbidity estimates. This could be done by assessing the number of individuals with morbidity at district or village level using local prevalence of infection data and comparing these estimates to morbidity data from registries in the same district or village. The developed methodology can also be applied to estimate the number of individuals with signs and symptoms due to other infectious

diseases, particularly those in which development of disease depends on the intensity of infection, e.g. anaemia due to hookworm infection.

10.2 Case management for schistosomiasis

In Part II of this thesis, we presented the results of our studies on schistosomiasis case management in health care facilities of Ghana, Mali and Senegal. The health systems in the three countries have a different history and policy for schistosomiasis control. Ghana does not have a national policy for integrated control, whereas Mali has a national schistosomiasis control program since 1982 and is in the process of shifting from vertical to integrated control. Northern Senegal has been evaluated at the end of a project that aimed at improving integrated schistosomiasis control. In this part of the discussion, we compare the quality of schistosomiasis case management in the three countries using the results of Chapters 6, 7 and 8, and examine the differences between the countries and the advantages and disadvantages of passive case detection.

10.2.1 Results of the comparison of schistosomiasis control in Ghana, Mali and Senegal

The questionnaire method provided information on pre-requisites for treatment of schistosomiasis cases at the health care facility: (1) active knowledge of health workers about the presenting symptoms of schistosomiasis, (2) use and availability of diagnostic tests, (3) acquaintance with recommended treatment and dosage of the drug, and (4) availability praziquantel. Here we compare these prerequisites for schistosomiasis case management between the three countries and also include the outcomes of the clinical scenario study (Chapter 9).

The percentage surveyed hospitals, health centres and private clinics was not significantly different in Ghana, Mali and Senegal ($p = 0.43$). The number of health workers reporting presence of *S. haematobium* infection in the coverage area of their health care facility was somewhat higher in Senegal and Mali than in Ghana ($p = 0.11$). Endemicity of *S. mansoni* infection was also more often reported in Senegal and Mali than in Ghana ($p = 0.001$). In Ghana, 21% of the health workers could not even recall about the existence of *S. mansoni* and were considered unaware of the presence of *S. mansoni* in their coverage area.

Active knowledge of the main presenting symptom of *S. haematobium*, haematuria, was good in the three surveyed countries. In Ghana and Mali, the clinical scenarios with *S. haematobium* symptoms often received urinary schistosomiasis as initial diagnosis. The main presenting symptoms of *S. mansoni* infection, blood in stool and abdominal pain, were less often mentioned than those of *S. haematobium* infection in all three countries. They were mentioned by more health workers in Senegal and Mali than in Ghana ($p < 0.001$). The two clinical scenarios with symptoms of *S. mansoni* infection were rarely diagnosed as intestinal schistosomiasis patients in the two surveyed countries. Dysuria was more often mentioned by health workers in Mali (63%) than those in Ghana (46%) and Senegal (33%) ($p = 0.004$) when health workers were requested to mention symptoms caused by *S.*

haematobium infection, whereas there was no significant difference in the frequency that pelvic discomfort was reported (approximately 45%).

First level health care facilities in endemic areas in Ghana would more often request a diagnostic test to confirm the symptom-based diagnosis 'urinary schistosomiasis' for patients presenting with haematuria than in Mali and Senegal (respectively 74, 17 and 31%, $p < 0.001$). Also for the two clinical scenarios with symptoms of *S. haematobium* infection diagnostic tests were twice as often requested by the Ghanaian health workers than by health workers in Mali. For patients presenting with blood in stool or bloody diarrhoea and suspected of *S. mansoni* infection, 67% of the first level health care facilities in Ghana, 44% in Mali and 38% in Senegal would confirm the diagnosis by requesting a diagnostic test ($p = 0.34$). Referral for a diagnostic test adds to the risk of non-compliance, as not all patients will comply with a referral due to time and money constraints. All laboratories reported use of the urine centrifugation test for diagnosing *S. haematobium* infection, only in Senegal four health care facilities reported to use the more specific urine filtration test. The equipment and material necessary for performing these tests was in stock at the moment of the interview. Seven health care facilities in Senegal reported to perform the Kato-Katz faecal smear test for diagnosing *S. mansoni* infection in their laboratory. Six of them had the necessary materials in stock. The other two countries exclusively used the direct smear test for diagnosing *S. mansoni*, and not the WHO recommended more sensitive Kato-Katz test. It should be noted that the diagnostic tests used (especially the urine centrifugation test and the direct smear test) have a low sensitivity and will therefore leave infected individuals undiagnosed.

Fewer health workers would prescribe praziquantel for treatment of *S. haematobium* infection in Ghana than in Mali and Senegal ($p < 0.001$), Table 10.3. Thirty-five percent of

Table 10.3: Prescription of praziquantel for *S. haematobium* or *S. mansoni* infection and availability in health care facilities (%) with reported endemicity of *S. haematobium* or *S. mansoni* in Ghana, Mali and Senegal.

	S. haematobium			*S. mansoni*		
	Ghana (n=49)	Mali (n=50)	Senegal (n=50)	Ghana (n=12)	Mali (n=22)	Senegal (n=26)
Prescription of praziquantel	53	98	100	92	86	100
Prescription of praziquantel and praziquantel in stock	22	78	72	50	68	73
Prescription of praziquantel at 40 mg kg^{-1} body weight and praziquantel in stock	12	72	63	25	64	62

the Ghanaian health workers in schistosome endemic areas reported to refer their patients for prescription of *S. haematobium* treatment: Although praziquantel is expected to be available at all levels of the health system, health workers at first level health care facilities often supposed that they were not allowed to prescribe praziquantel themselves. Both for treatment of *S. haematobium* and *S. mansoni* infection praziquantel was often not in stock,

and the recommended dosage of 40 mg kg^{-1} body weight was not always prescribed by the Ghanaian health workers.

The total costs of treatment for schistosomiasis converted to Euros differed slightly between the three countries and was lowest in Senegal and highest in Mali (Figure 10.1). Costs of treatment corrected for purchasing power differences[2] (relative costs) were highest in Ghana and lowest in Senegal. The costs are considerable compared to the corrected GNP per capita (Ghana 1,964, Mali 849 and Senegal 1,510 international $, http:\\devdata.worldbank.org) and are likely to be too high for individuals suffering from symptoms of schistosomiasis. Indeed, 'not having money' was one of the main reasons for not visiting a health care facility for symptoms related to schistosome infection in a survey in Southern Ghana, but individuals from higher social classes did not visit health care facilities more often for symptoms such as haematuria and blood in stool (Danso-Appiah *et al.*, 2001).

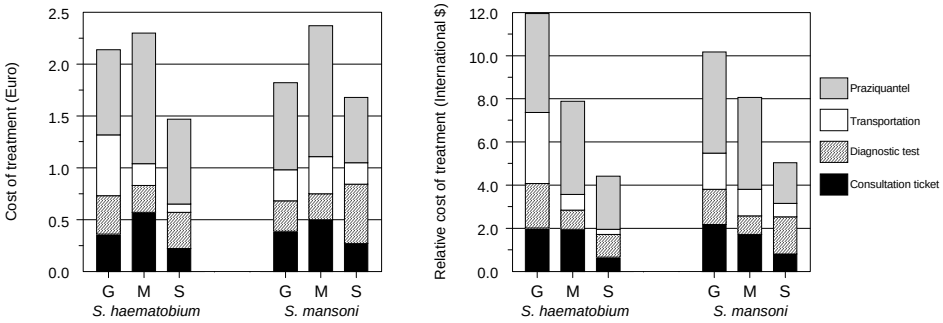

Figure 10.1: Costs (converted to Euros) and relative costs (converted to international $) of treatment for schistosomiasis in areas reported endemic in Ghana (G), Mali (M) and Senegal (S).

In conclusion, pre-requisites for schistosomiasis case management were less favourable in Ghana than in Mali and Senegal. Patients were more often referred for a diagnostic test or for treatment, which enlarges the risk of non-compliance and increases the total costs of treatment due to extra transportation costs. The main difference between Ghana and the other two countries is that there is no (national) schistosomiasis control program and that in most parts of the county schistosomiasis has never received special attention. The special project that aimed at improving integrated schistosomiasis control in Senegal proves that it is possible to reach high levels of passive case detection within a relatively short time. Therefore, implementing a schistosomiasis control program or policy in the

[2] Conversion from local currency to international $ using purchasing power parity conversion factor 716.2 for Ghana, 189.4 for Mali and 216.4 for Senegal (http://www.worldbank.org/data/icp/pppdata.htm, accessed 21-11-2002)

Ghanaian health system might seriously improve the chance of adequate treatment for patients reporting with symptoms caused by schistosome infection at a health care facility.

10.2.2 Measuring quality of case management

It is clear that a considerable number of health workers would not treat the clinical scenarios presented in Chapter 9 as schistosomiasis cases, especially those resulting from *S. mansoni*. However, this does not necessarily mean low quality of case management as the scenarios might just as well represent patients with other diseases. In an attempt to evaluate the general quality of the answers of the health workers, we presented the answers given by the health workers for the clinical scenarios to four experts (medical doctors) with experience in primary health care in Ghana and four in Mali. They were requested to give their opinion about the initial diagnosis suggested by the health workers and the prescribed treatment (if direct treatment was performed) for the four clinical scenarios. Each different initial diagnosis was judged as 'good', 'sub-optimal' or 'incorrect' by the experts. If no diagnosis was given by the health worker it was scored as incorrect. Thereafter, they were asked to assess the quality of the prescribed treatment in the same categories. The quality of the initial diagnosis and the prescribed treatment of a health worker for a clinical scenario was appraised as adequate if at least three of the four experts judged the suggested initial diagnosis or prescribed treatment as 'good' or 'sub-optimal', else it was appraised as inadequate.

Malian experts judged the answers of the Malian health workers for the initial diagnosis of clinical scenario A, B, C and D in general as adequate (Figure 10.2). Also, the answers from the Ghanaian health workers were usually considered adequate, except for scenario D where only 33% of the health workers mentioned an adequate initial diagnosis according to the experts. For this scenario, the experts considered only malaria or food poisoning a good initial diagnosis. The quality of the prescribed treatment was in general assessed less favourable by the experts compared to the initial diagnosis, especially direct treatment for scenario C in Mali was considered incorrect if antibiotics or metronidazole was included in the treatment. The Malian experts considered schistosomiasis an adequate initial diagnosis for all four scenarios. Treatment with praziquantel was also judged as an adequate strategy. Ghanaian experts considered schistosomiasis as an adequate initial diagnosis for scenarios A, B and C, but not for D. Praziquantel treatment was regarded as adequate treatment for scenario A and B.

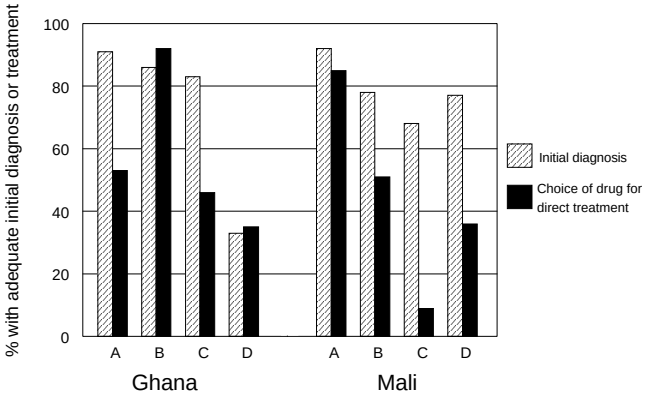

Figure 10.2: Percentage of the interviewed health workers in Ghana and Mali receiving an adequate score from experts for the initial diagnosis (diagnosis) and prescribed direct treatment (choice of drug for direct treatment) for four clinical scenarios. Scores were attributed to reported initial diagnosis and the situations where direct treatment would be given. Scenarios A and B refer to *S. haematobium* and C and D to *S. mansoni* cases, for detailed description of clinical scenarios see Chapter 9.

The assessment of the quality of answers by the health workers was complicated by the considerable variation in the judgement of the experts. Some experts were consistently more disapproving in their judgements than others and there was often no consensus. For example, amoebiasis was considered an adequate initial diagnosis for scenario B by one Ghanaian expert, sub-optimal by another and two considered it inadequate. Also, the Malian experts often disagreed about the quality of the answers. For example, two experts judged treatment of scenario C with praziquantel as good, one sub-optimal and one incorrect. In about 45% of the answers given, the experts considerably disagreed in their judgements; in these cases the same answer was at least assessed once as good and once incorrect. For Ghana, two experts considered almost all answers as incorrect, two others rarely considered an answer as incorrect, in Mali the judgements were more evenly distributed. Future studies should therefore use more detailed instructions about how to judge the answers of the health workers to prevent dissimilar decision making processes or use the Delphi method to come to a group consensus (Milholland *et al.*, 1973). Quality of case management can also be assessed by relating answers for the presented clinical scenarios to national or international (see below *10.2.3*) guidelines for case management.

10.2.3 Case management compared to the WHO recommendations

A strategy for diagnosing schistosomiasis (either on symptoms or with a test) and for treatment by the health care system was put forward by the WHO Expert Committee on the Control of Schistosomiasis in 1991 (WHO, 1993) and maintained in the most recent report (WHO, 2002), see Box.

WHO recommendations for diagnosis and treatment of schistosomiasis by the health system:

1) Symptomatic cases should be treated with praziquantel at all levels of the health system

2) If diagnostic facilities are not available in the health care facility, case detection should be performed on presenting symptoms (symptom-based treatment), i.e. direct prescription of praziquantel

3) If a laboratory is available, sensitive diagnostic tests (e.g. urine filtration or centrifugation for *S. haematobium* and Kato Katz faecal smear for *S. mansoni*) should be used for diagnosis

The quality of schistosomiasis case management measured by the clinical scenario method (answers of health workers that reported urinary schistosomiasis as initial diagnosis for scenario A) and the questionnaire method was comparable. Our studies showed that if prescribing treatment WHO recommendation 1 was followed by most health workers in Mali and Senegal (Figure 10.2). Ghanaian health workers at first level health care facilities often referred patients suspected of *S. haematobium*, because they believed that they were not allowed to treat *S. haematobium* patients themselves. Less health workers complied with recommendation 2 (direct treatment if diagnostic facilities are not available). Especially Ghanaian health workers reported to refer schistosomiasis patients for a diagnostic test. Recommendation 3 was followed by all health workers in Ghana and Mali for *S. haematobium* and by respectively 88 and 100% for *S. mansoni*. In Senegal approximately 40% of the health care facilities with a laboratory performed a diagnostic test. This low utilisation rate is probably an effect of the project that aimed at symptom-based treatment of patients presenting with symptoms caused by schistosome infection.

Although health care facilities without laboratory facilities should not perform a diagnostic test to confirm *S. mansoni* diagnosis according to WHO recommendation 2, it is difficult to diagnose *S. mansoni* infection on symptoms because they are not specific and may very well be caused by other diseases. Therefore, depending on the epidemiological situation in the coverage area of the health care facility, we think that presumptive treatment (in areas with high endemicity of *S. mansoni*) or requesting a diagnostic test (in areas with low endemicity of *S. mansoni*) can be considered the most effective case management policy for patients suspected of *S. mansoni* infection.

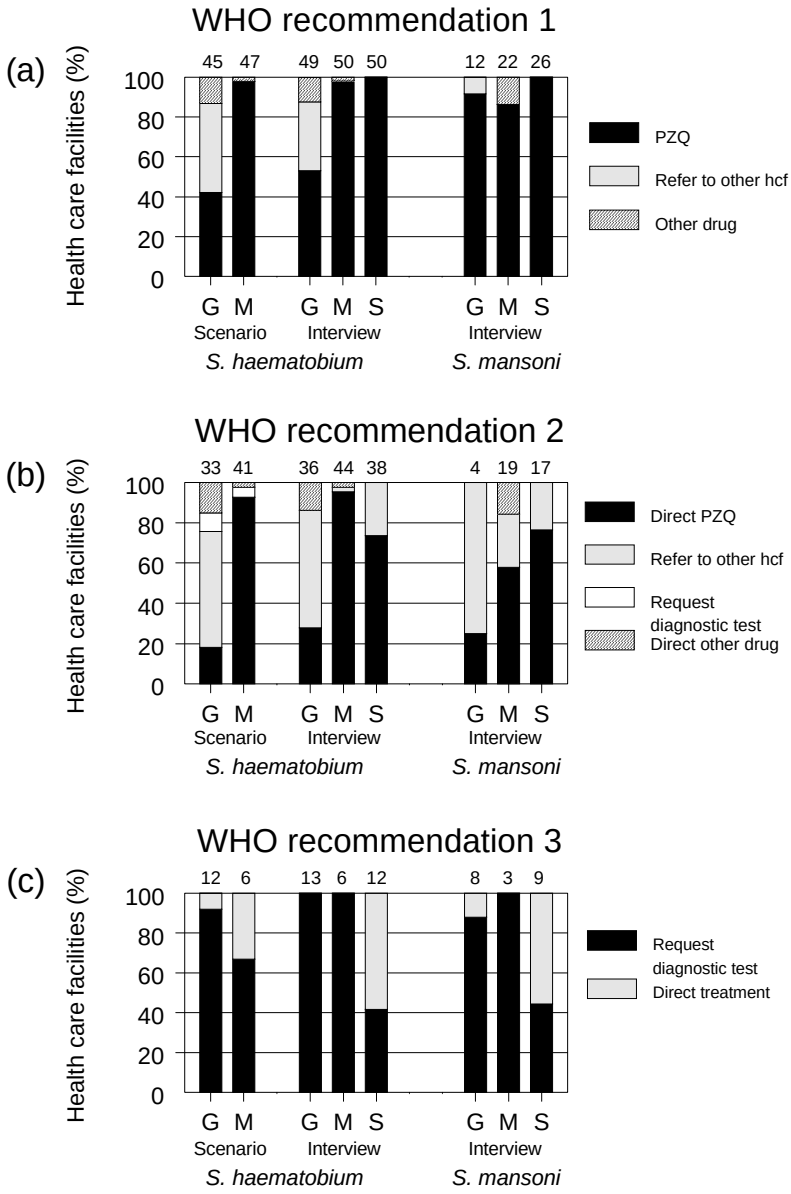

Figure 10.2: Adoption of WHO recommendation 1 by all health care facilities (a), 2 by health care facilities without laboratory facilities (b) and 3 by health care facilities with laboratory facilities (c), for passive schistosomiasis case detection and treatment in endemic areas in Ghana (G), Mali (M) and Senegal (S) determined by the clinical scenario method (Scenario A) and the questionnaire method (Interview). ▮ is according to the WHO recommendation (see Box). The numbers above the bars indicate the number of health workers mentioning *S. haematobium* as diagnosis for scenario A (Scenario) and the number of health workers reporting presence of *S. haematobium* or *S. mansoni* in the coverage area of the health care facility (Interview).

10.2.4 Passive vs. active case detection

'Adequate diagnosis and treatment of patients with symptomatic schistosomiasis is the primary component of any morbidity control programme' (cited from (WHO, 1993)). Schistosomiasis case management requires functioning of the last two steps in the passive case detection process, i.e. *disease – health care visiting – treatment (within the health system)* (Figure 1.3). As an example we calculated the chance that a Ghanaian patient with haematuria or blood in stool receives praziquantel. In a recent study in Southern Ghana, 30% of the individuals with haematuria in the last month reported to seek health care and only approximately 50% of them visited the regular health services (Danso-Appiah *et al.*, submitted). Then about 60% will receive a prescription for praziquantel and in 50% of the health care facilities where praziquantel is prescribed it was also in stock (Chapter 9). Thus a patient with haematuria in Ghana has 4.5% chance of receiving praziquantel if he/she has or had haematuria in the last month (30% × 50% × 60% × 50%). The same calculations for blood in stool result in a 1.5% chance of receiving praziquantel for individuals with blood in stool in the last month (60% × 25% × 15% × 65%). Although we consider these chances to be low, it is possible that individuals have many episodes of haematuria or blood in stool and will still have a reasonable probability of receiving praziquantel at least a few times in their lives. These few treatments might be sufficient for preventing the development of serious morbidity (WHO, 2002). However, it is likely that many patients never visit a health care facility for symptoms caused by schistosome infection and therefore never receive treatment. Also, patients most likely always visit the same (nearby) health care facility. If schistosomiasis case management is not adequate in that facility and praziquantel not in stock, they still have a low chance of receiving adequate treatment. These individuals remain at risk of developing serious symptoms. The effect of passive case detection could be increased by health education of the population (informing them to seek health care at regular health services for symptoms), improved case management in the health care facilities and increasing the availability of praziquantel.

Another strategy, regular chemotherapy of high-risk groups (children or occupational groups), is now promoted by the joined WHO Expert Committees on the Prevention and Control of Schistosomiasis and Soil-transmitted Helminthiasis (WHO, 2002). This could be performed by the existing health structures (integrated in the routine health services), by school health programmes and by community-based drug delivery programmes. It will certainly be less expensive and more sustainable than mass treatment by mobile teams. Treatment of high risk groups with screening only requires adequate techniques for identifying infected individuals. If no screening is applied, success of the control programme does not depend on the elements introduced in Figure 1.3. Compared to passive case detection, these strategies probably have a higher potential to cover large groups of affected individuals, but also include the risk of poor coverage.

We subscribe to the recommendations of the WHO for passive case detection (see Box). Still the effect of passive case detection through health services on morbidity control is probably limited in particular due to low health care seeking for symptoms caused by *S.*

haematobium infection, low alertness of health workers about symptoms due to *S. mansoni* infection and poor availability of praziquantel in peripheral health structures. Thus, other morbidity control efforts remain necessary. However, we consider it unacceptable if praziquantel is only available from such efforts (i.e. school or community-based drug delivery programmes) and not in the official health services, as this would seriously undermine the role of the health system in providing health care for three reasons. First, it makes treatment of schistosomiasis less effective if patients can only receive praziquantel during mass treatment campaigns and not via the health system. In fact, this sometimes creates the paradoxical situation in which individuals without symptoms are treated during mass treatment campaigns and patients who developed symptoms in between are unable to obtain treatment. Second, tools for providing health care are limited in most schistosome endemic countries. If health care facilities are not supplied with praziquantel and for example only schools have it in stock, it is understandable that this will reduce the motivation of health workers for treatment of schistosomiasis and probably also for other diseases. Third, if patients with symptoms caused by schistosome infection do not visit the health system (because praziquantel is not available) an opportunity is lost to give individually tailored information on schistosomiasis and also about other diseases. Also, if praziquantel is available in the health care facility, health workers can use it for treatment of high risk groups that visit the facility regularly e.g. for vaccinations or antenatal care.

10.2.5 Possibilities for further research on case management of schistosomiasis

The clinical scenarios were not presented to health workers in Senegal. This is interesting to obtain a complete overview of case management in the three West African countries. Furthermore, returning to Senegal would give us the opportunity to interview the same respondents again using our structured questionnaire. This will give information about sustainability of the effects after the end of the project that aimed at improving integrated schistosomiasis control. Do health workers still know the symptoms of schistosomiasis more than 7 years after the start of the project (compared to after two years)? Is praziquantel still available?

The clinical scenario method has only been used in a few studies. Validation of this method and assessment of the differences in outcomes compared to methods such as observations or the use of simulated patients is needed. For example, after randomising the health care facilities into two groups, health workers in group 1 first receive simulating patients and then the clinical scenarios, and for group 2 the other way around. For studying the effect of study method, both simulating patients and clinical scenarios should present with the same symptoms. This is feasible because health workers will probably not ask the simulating patients to show their bloody urine or stools. For example for STDs this was more problematic as persons simulating STD symptoms were regularly asked for a physical examination and had to avoid or refuse this (Voeten *et al.*, 2001).

Combining the information from the questionnaire studies and the clinical scenarios reveals the chance of receiving treatment with praziquantel for a schistosomiasis patient

when presenting at a health care facility. In Southern Ghana, information was collected about health care seeking behaviour for symptoms caused by schistosome infection: (1) Do patients seek health care? and (2) Which health care facilities do they visit? (Danso-Appiah *et al.*, submitted). This enabled us to calculate the chance that an individual with symptoms from schistosome infection will receive adequate treatment. It is questionable if the results of the health care seeking behaviour study in Southern Ghana can be extrapolated to countries with a longer history of schistosomiasis control (Mali and Senegal). This has to be investigated, preferably using a similar study design.

10.3 Conclusions

- The burden of schistosomiasis is higher than suggested by the calculations of the Global Burden of Disease Initiative published for 1990.
- The number of deaths due to schistosomiasis seems to be substantially higher than usually presumed. However, our estimates have been based on limited evidence and can be improved upon if data from death registries using standardised methods for determining the cause of death become available.
- The methodology that has been developed to estimate the number of individuals with schistosomiasis signs and symptoms can also be applied for other infectious diseases, particularly those in which development of disease depends on the intensity of infection as in most helminth infections.
- Schistosomiasis case management (passive case detection) by the regular health system should be the primary component of a schistosomiasis control programme. It would be unacceptable if knowledge of schistosomiasis treatment and drugs are available in other sectors (e.g. schools and companies) and not in the health sector.
- Passive case detection by the health care facilities is currently not sufficient to come to effective morbidity control. This is because of low tendency to seek health care (especially for *S. haematobium*), low alertness of health workers for the presenting symptoms (especially for *S. mansoni*) and poor availability of praziquantel in peripheral health structures. Poor physical and financial accessibility of the health services also affects passive case detection.
- Programs to train staff and make praziquantel available can improve functioning of health systems for schistosomiasis case management, as is exemplified by Senegal and Mali.

In view of the increasing interest of the international community for schistosomiasis control and treatment of patients via health systems (in particular the recently started Schistosomiasis Control Initiative funded by the Bill and Melinda Gates Foundation), it would be interesting to apply the methodologies presented in this thesis for studying burden of schistosomiasis and evaluating case management in other endemic regions and countries.

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Summary

Schistosomiasis is one of the most prevalent parasitic infections and an important public health problem in many developing countries. The main early symptom of *Schistosoma haematobium* infection is blood in urine (haematuria) and *S. mansoni* infection causes bloody diarrhoea. The symptoms are caused by eggs that get trapped while migrating from the blood vessels of the urinary or intestinal tract through the wall of the bladder or intestines. After prolonged infection, severe pathological changes may develop such as hydro-ureter and hydronephrosis in individuals infected with *S. haematobium* and ascitis and haematemesis in individuals infected with *S. mansoni*. Current estimates of the number of individuals with symptoms and the burden of disease due to schistosome infection lack detail and precision and are considered to be too low. Therefore, we aimed at determining more accurate estimates using data from published field studies in Part I of this thesis.

In **Chapter 2**, we developed a method to associate prevalence of schistosome infection with prevalence of morbidity in a population. In this chapter, we showed the resulting associations for morbidity due to *S. mansoni* infection. The associations suggested that diarrhoea and blood in stool due to *S. mansoni* infection mainly occurs in communities with the highest prevalence of infection (>70%). Whereas an influence on hepatosplenic morbidity was already present at low community prevalence of infection. For the aspecific symptom abdominal pain we could not find an association. The data did not indicate different associations for schools and communities. Similar associations derived for *S. haematobium* infection and bladder pathology (by ultrasound) and haematuria (by reagent strips, questionnaires or inspection of a urine sample) were the subject of **Chapter 3**. All four methods to detect early pathology and morbidity showed a clear association with prevalence of *S. haematobium* infection. Also, as expected, prevalence of micro-haematuria by reagent strip was higher than that of macro-haematuria by questionnaire, which was again higher than macro-haematuria by inspection. Study setting (school or community survey) had a clear impact on bladder wall pathology, but not on haematuria. This implies that ultrasound gives less often a positive outcome in adults compared to children with the same level of bladder pathology. In **Chapter 4**, we showed that the recall period length used in the questionnaires measuring self-reported haematuria had no effect on the association of prevalence of *S. haematobium* infection with haematuria. Finally, in **Chapter 5**, we used the associations between prevalence of schistosome infection and morbidity to estimate the number of individuals with schistosomiasis related morbidity in Africa. In total, 70 million individuals were estimated to experience haematuria, 32 million dysuria, 18 million major bladder wall pathology and 10 million major hydronephrosis associated with *S. haematobium* infection. Infection with *S. mansoni* was estimated to cause diarrhoea in

0.78 million individuals, blood in stool in 4.4 million and hepatomegaly in 8.5 million. In **Chapter 10.1** we calculated DALYs lost due to schistosomiasis using the estimated number of individuals with morbidity and death due to schistosomiasis. We made the conservative assumption that all severe symptoms are present in those individuals with milder symptoms. Also, symptoms about which no quantitative information was available (e.g. subtle morbidity) were not included in our calculations. In spite of this, we found that the burden of schistosomiasis is about three times higher than suggested by the Global Burden of Disease calculations published for 1990. If mortality is included in the calculations, our estimations are minimal four times higher.

Morbidity control is the main goal of most initiatives to control schistosomiasis. This became feasible after the introduction of praziquantel, an effective safe single dose drug. According to WHO recommendations, morbidity control should be integrated in the Primary Health Care system with at least adequate diagnosis and treatment of patients reporting with symptoms of schistosomiasis at the health system. In Part II of this thesis, we explored the quality of schistosomiasis case management and determined the probability that patients with symptoms from *S. haematobium* or *S. mansoni* infection that report at the health system receive adequate treatment.

In **Chapters 6**, **7** and **8**, we assessed whether the main prerequisites for diagnosis and treatment of schistosomiasis patients were available in the health care facilities by interviewing health workers employed at different levels of the health system in Ghana, Mali and Senegal using a structured questionnaire. We assessed knowledge of the presenting symptoms, treatment strategy and availability of diagnostic materials and drugs. Active knowledge of the main presenting symptom of *S. haematobium*, haematuria, was good. The main presenting symptom of *S. mansoni* infection, blood in stool, was less well known than that of *S. haematobium* infection in all three countries. Overall knowledge about schistosomiasis was best in Senegal and Mali. Diagnostic tests were frequently requested, also in health care facilities without a laboratory. Most laboratories used the urine centrifugation test for diagnosing *S. haematobium* infection. For diagnosis of *S. mansoni* infection the direct smear test was used, but several health care facilities in Senegal reported to perform the more sensitive Kato-Katz test. Praziquantel was more often prescribed for treatment of *S. haematobium* infection by health workers in Mali and Senegal than in Ghana. It was often not in stock in Ghana. In conclusion, pre-requisites for schistosomiasis case management were less favourable in Ghana than in Mali and Senegal. In **Chapter 9**, we studied schistosomiasis case management by presenting four clinical scenarios, two presenting with symptoms compatible with *S. haematobium* and two with symptoms compatible with *S. mansoni* infection, to health workers in Ghana and Mali. It appeared that patients reporting with *S. haematobium* symptoms can expect proper treatment at approximately 60% of the health care facilities, whereas those presenting with *S. mansoni* symptoms only have a very limited chance (about 15%). In **Chapter 10.2** we showed that a Ghanaian schistsomiasis patient has a very low chance of receiving

praziquantel. Therefore, it is questionable if passive case detection is a sufficient basis for effective schistosomiasis morbidity control. Still, we consider it an essential component of schistosomiasis control as it is unacceptable if knowledge of schistosomiasis treatment and drugs would be available in other sectors (e.g. schools and companies) and not in the health sector.

Samenvatting

Schistosomiasis is één van de meest voorkomende parasitaire infectieziekten en een belangrijk probleem voor de volksgezondheid in veel ontwikkelingslanden. Het voornaamste vroege symptoom als gevolg van infectie met de worm *Schistosoma haematobium* is bloed in de urine (hematurie). De eveneens veel in Afrika voorkomende worm *S. mansoni* leidt in een vroeg stadium tot bloederige diarree. Deze symptomen worden veroorzaakt door eieren die tijdens de migratie van de bloedvaten van het urinewegsysteem of de darmen naar de urine of ontlasting blijven steken in de blaas- of darmwand. Als de infectie langere tijd bestaat dan kunnen ernstige pathologische veranderingen ontstaan zoals verwijding van de urineleider of de nierbekkens in mensen die geïnfecteerd zijn met *S. haematobium* en vocht in de buikholte en bloed braken in mensen met *S. mansoni*. Bestaande schattingen van het aantal mensen met symptomen zijn zeer onnauwkeurig. De door de Global Burden of Disease geschatte ziektelast in DALYs (som van het aantal verloren levensjaren en het aantal jaren geleefd met een belemmering door de ziekte) door infectie met schistosomen wordt als te laag beschouwd. Daarom proberen wij in **Deel I** van dit proefschrift het aantal mensen met morbiditeit door schistosomiasis nauwkeuriger te schatten met een nieuwe methode die gebruik maakt van informatie uit gepubliceerde veldstudies.

In **Hoofdstuk 2** presenteren we de analyse methode, die gebaseerd is op de associatie tussen de prevalentie van schistosome infectie en de prevalentie van morbiditeit. De associaties voor verschillende vormen van morbiditeit door infectie met *S. mansoni* worden in dit hoofdstuk gegeven op basis van 9 tot 43 gepubliceerde veldstudies. De resultaten laten zien dat de door *S. mansoni* veroorzaakte diarree en bloed bij de ontlasting vooral worden gevonden bij populaties met de hoogste prevalentie van infectie (>70%). Vergroting van de lever en milt wordt ook gevonden bij bevolkingsgroepen met een lagere prevalentie van infectie. Voor het aspecifieke symptoom buikpijn konden we geen associatie aantonen. In **Hoofdstuk 3** zijn op dezelfde manier associaties bepaald voor *S. haematobium* infectie en blaaspathologie (gediagnosticeerd met echografie) en hematurie (gediagnosticeerd m.b.v. teststrips, vragenlijsten of door inspectie van urine) op basis van 8 tot 21 gepubliceerde veldstudies. De vier methoden, waarmee vroege pathologie en morbiditeit gediagnosticeerd wordt, hebben alle een duidelijke associatie met *S. haematobium* infectie prevalentie. Zoals verwacht is de met teststrips gediagnosticeerde prevalentie van micro-hematurie hoger dan die van macro-hematurie gediagnosticeerd met vragenlijsten. Deze is weer hoger dan macro-hematurie gemeten door inspectie van urine. De gevonden prevalentie blaaspathologie is duidelijk verschillend voor studies in scholen of in dorpen, terwijl er geen verschil was voor hematurie. Dit suggereert dat echografie minder vaak een positieve uitslag geeft bij volwassenen dan bij kinderen met de zelfde

graad van pathologie. In **Hoofdstuk 4** tonen wij aan dat de associatie tussen *S. haematobium* infectie prevalentie en gerapporteerde hematurie niet verschillend is voor onderzoeken die naar hematurie in de afgelopen 2 weken of in de afgelopen 4 weken vragen. Tenslotte worden in **Hoofdstuk 5** m.b.v. de associaties tussen *Schistosoma* infectie en morbiditeit uit hoofdstuk 2 en 3, en de aanwezigheid van infectie in Afrikaanse populaties gebaseerd op gepubliceerde GIS (Geographic Information System) schattingen, het aantal mensen met morbiditeit door schistosomiasis in Afrika berekend. Wij schatten dat 70 miljoen mensen hematurie hebben door *S. haematobium* infectie, 32 miljoen pijn bij het plassen, 18 miljoen ernstige blaaswand pathologie en 10 miljoen ernstige nierafwijkingen (hydronephrose). Infectie met *S. mansoni* veroorzaakt diarree bij 0.78 miljoen mensen, bloed bij de ontlasting bij 4.4 miljoen en leververgroting bij 8.5 miljoen. Voorzichtige schattingen, gebaseerd op slechts een beperkt aantal artikelen, suggereren dat het aantal doden door infectie met schistosomen in de buurt van de 200-300 duizend ligt. In **Hoofdstuk 10.1** bespreken we deze resultaten in meer detail en hebben we het verlies aan DALYs door schistosomiasis berekend. Voor de berekeningen gebruiken we de conservatieve aanname dat mensen met ernstige symptomen ook mildere symptomen hebben en alleen het verlies aan DALYs door de ernstige symptomen is dan in de berekeningen opgenomen. Symptomen waarvan geen kwantitatieve informatie beschikbaar is (zoals de regelmatig gesuggereerde vermindering van de groei van kinderen) zijn niet in onze berekeningen opgenomen. Desondanks is de door ons berekende ziektelast t.g.v. schistosomiasis ongeveer drie keer zo hoog als in 1990 gepubliceerde 'Global Burden of Disease' berekeningen. Als we sterfte in de berekeningen meenemen zijn onze schattingen zelfs vier maal hoger.

Het voorkomen van morbiditeit is het belangrijkste doel van veel schistosomiasis bestrijdingsprogramma's, nadat vele pogingen tot langdurige reductie van transmissie niet succesvol zijn gebleken. Hiertoe is praziquantel, een veilig en effectief medicijn, beschikbaar. Volgens de aanbevelingen van de Wereldgezondheidsorganisatie (WHO) moet de bestrijding worden geïntegreerd in de basisgezondheidszorg. Dit betekent in ieder geval dat adequate diagnose en behandeling aanwezig moeten zijn voor patiënten die zich met klachten van schistosomiasis melden bij een kliniek of gezondheidspost. In **Deel II** van dit proefschrift kijken we naar de kwaliteit van de behandeling voor schistosomiasis patiënten en bepalen we de kans dat patiënten met symptomen door *S. haematobium* of *S. mansoni* infectie die zich melden bij het gezondheidszorgsysteem adequate behandeling krijgen. Deze studie maakt deel uit van een door WOTRO/NWO gefinancierd onderzoeksprogramma naar geïntegreerde bestrijding van schistosomiasis in Ghana, Mali en Senegal.

In de studies die beschreven zijn in de **Hoofdstukken 6**, **7** en **8** onderzoeken we of de belangrijkste voorwaarden voor diagnose en behandeling van schistosomiasis patiënten aanwezig zijn in klinieken, gezondheidsposten en ziekenhuizen. Dit hebben we gedaan door gezondheidswerkers van gezondheidsposten, ziekenhuizen en privé klinieken in

respectievelijk Ghana (n=70), Mali (n=60) en Senegal (n=55) te interviewen m.b.v. een gestructureerde vragenlijst. Daarbij bepaalden we de kennis van de belangrijkste symptomen, behandelingsstrategieën en de aanwezigheid van praziquantel en materialen voor diagnostiek. Het belangrijkste symptoom van *S. haematobium* (hematurie) blijkt bekend bij de meeste gezondheidswerkers. In alle drie de landen is het belangrijkste symptoom van *S. mansoni* infectie (bloed bij de ontlasting) veel minder goed bekend. Over het algemeen is de kennis van schistosomiasis het beste in Senegal en Mali. In die twee landen is in de voorgaande jaren veel meer aandacht geweest voor onderzoek en bestrijding dan in Ghana. Diagnostische testen worden frequent aangevraagd, ook in klinieken zonder laboratorium, wat extra kosten en uitval betekent. De meeste laboratoria gebruiken de urine centrifugatie test voor het diagnosticeren van *S. haematobium* infectie. Voor de diagnose van *S. mansoni* infectie wordt het directe feces preparaat gebruikt, en maar enkele klinieken (in Senegal) rapporteren het gebruik van de gevoeliger en door WHO aanbevolen Kato-Katz test. Praziquantel wordt in Mali en Senegal vaker voorgeschreven voor de behandeling van *S. haematobium* infectie dan in Ghana en is in het laatst genoemde land vaak niet eens verkrijgbaar. Uit deze studies concluderen wij dat de voorwaarden voor behandeling van schistosomiasis patiënten gunstiger zijn in Mali en Senegal dan in Ghana, maar gerichte interventies zoals beschreven voor Senegal in hoofdstuk 8 kunnen veel verbeteren. Uiteraard hoeft in de gevallen dat kennis van de ziekte en de juiste diagnostische materialen en medicijnen beschikbaar zijn, dit nog niet te betekenen dat patiënten met schistosomiasis daadwerkelijk adequate zorg krijgen. In **Hoofdstuk 9** hebben wij daarom de behandeling van schistosomiasis patiënten bestudeerd door vier beschrijvingen van hypothetische patiënten aan gezondheidswerkers in Ghana en Mali voor te leggen, twee die het gevolg zouden kunnen zijn van *S. haematobium* en twee van *S. mansoni* infectie. Deze studie laat zien dat in beide landen patiënten die zich bij het gezondheidssysteem melden met *S. haematobium* symptomen in ongeveer 60% van de klinieken de juiste behandeling zullen krijgen. Patiënten die zich presenteren met symptomen van *S. mansoni* infectie hebben maar een kleine kans op adequate behandeling (ongeveer 15%). Dit laatste hoeft niet altijd een probleem te zijn omdat de verschijnselen door *S. mansoni* ook door andere (infectie) ziekten zouden kunnen komen. In **Hoofdstuk 10.2** berekenen we dat schistosomiasis patiënten een erg lage kans hebben om behandeld te worden met praziquantel, in de eerste plaats omdat ze een kleine kans hebben om de juiste behandeling te krijgen (dit proefschrift) maar ook omdat ze m.n. bij *S. haematobium* geen behandeling zoeken voor hun symptomen (uitkomst van veldstudie binnen hetzelfde onderzoeksprogramma). Daarom is het twijfelachtig of morbiditeit door schistosome infectie voorkomen kan worden door uitsluitend behandeling van patiënten die zich zelf melden bij een gezondheidspost, ziekenhuis of privé kliniek. Toch beschouwen we het als een essentieel onderdeel van een schistosomiasis bestrijdingsprogramma. We vinden het onacceptabel als medicijnen en kennis nodig voor de behandeling van schistosomiasis aanwezig zijn in andere sectoren (b.v. scholen en bedrijven) en niet in de gezondheidssector.

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Curriculum vitae

Marieke J. van der Werf was born on August 17, 1971 in Gouda (The Netherlands). In 1989, she passed her secondary school exam at the St. Maartenscollege in Voorburg and began studying Biomedical Sciences at the University of Leiden. From 1991, she simultaneously studied Medicine, also in Leiden. During these studies she carried out three research projects: (1) at the department of Gastroenterology-Hepatology, University Hospital Leiden; (2) at the department of Parasitoloy, University of Leiden and the Région Médicale St Louis, Senegal; and (3) at the department of Clinical Viro-Immunology, Central laboratory of the Netherlands Red Cross, Amsterdam. In September 1997, she graduated in Biomedical Sciences and Medicine. Thereafter, she worked as a medical doctor and researcher at the municipal health service in Amsterdam (division of Public Health and Environment) within the framework of the 'Amsterdam cohort studies on HIV infection and AIDS'. In March 1999, she became a PhD student (funded by NWO/WOTRO) at the department of Public Health, Erasmus MC Rotterdam. Her research project was on the control of schistosomiasis in West Africa and contained three field work periods during which she performed research on the health systems of Ghana, Mali and Senegal in collaboration with the Noguchi Memorial Institute for Medical Research, the Institut National de Recherche Santé Publique and the Région Médicale St Louis, respectively. She also performed a project at the World Health Organization in Geneva (department of Communicable Diseases Control, Prevention and Eradication). In June 2001, she obtained her Master of Public Health degree at the Netherlands School of Public Health in Utrecht. Since February 1, 2003, she is senior epidemiologist at the Royal Netherlands Tuberculosis Association (KNCV) in The Hague.

Curriculum vitae

Marieke J. van der Werf werd op 17 augustus 1971 in Gouda geboren. In 1989 behaalde zij haar VWO-diploma (Atheneum B) op het St. Maartenscollege te Voorburg. In datzelfde jaar begon zij met de studie Biomedische wetenschappen aan de Universiteit Leiden. Daarnaast begon zij in 1991 met de studie Geneeskunde, eveneens in Leiden. Tijdens de doctoraalfase van de studie Biomedische wetenschappen deed zij drie onderzoeksstages. De eerste stage was bij Gastroenterologie en Hepatologie in het Leids Universitair Medisch Centrum (LUMC) in Leiden, de tweede bij de vakgroep Parasitologie van de Universiteit Leiden met een veldwerk periode bij de Région Médicale St. Louis in Senegal en de derde bij de afdeling Klinische Viro-Immunologie van het Centraal Laboratorium van het Nederlandse Rode Kruis (CLB) in Amsterdam. In september 1997 behaalde zij haar doctoraal diploma Biomedische wetenschappen en deed zij artsexamen. Aansluitend werkte zij als arts-onderzoeker bij de GG&GD in Amsterdam op de afdeling Volksgezondheid en Milieu aan de 'Amsterdam cohort studies on HIV infection and AIDS'. In maart 1999 begon zij aan haar promotie-onderzoek als Onderzoeker in Opleiding (OIO) bij het Instituut Maatschappelijke Gezondheidszorg (MGZ), Erasmus MC Rotterdam, op een project gefinancierd door NWO/WOTRO. Haar onderzoek betrof de bestrijding van schistosomiasis in West Afrika. Dit bevatte 3 veldwerkperioden waarin onderzoek werd verricht aan de gezondheidssystemen van Ghana, Mali en Senegal in samenwerking met het Noguchi Memorial Institute for Medical Research, het Institut National de Recherche Santé Publique en de Région Médicale St Louis. Daarnaast deed zij een ondezoeksproject bij de afdeling Communicable Diseases Control, Prevention and Eradication van de Wereldgezondheidsorganisatie (WHO) in Genève. In 2001 behaalde zij het Master of Public Health diploma aan de Netherlands School of Public Health in Utrecht. Vanaf 1 februari 2003 is zij werkzaam als senior epidemiologisch onderzoeker bij de Koninklijke Nederlandse Vereniging tot bestrijding der Tuberculose (KNCV) in Den Haag.

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