Novel approaches in the control of schistosomiasis:
from rapid identification to chemoprophylaxis

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Jürg Utzinger

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Herren Prof. Dr. M. Tanner und Prof. Dr. L. Jenni

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Prof. Dr. A. Zuberbühler

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Summary

Human schistosomiasis is the second most prevalent parasitic disease in the tropics, and has a huge impact on public health and socio-economic development. It is estimated that 652 million people live at risk of infection and that 193 million people are actually infected. Of the 120 million symptomatic cases, 20 million are suffering from severe disease. At present, 85% of all these cases are concentrated in sub-Saharan Africa and they cause an estimated morbidity burden of 3.5 million disability adjusted live years (DALYs). Since the advent of safe, effective, single dose drugs, the emphasis in schistosomiasis control has been on morbidity control. Since praziquantel is active against all schistosome species and has become relatively inexpensive, it is used as the drug of choice. For effective control of schistosomiasis, it is now of central importance to make the drug available to the communities at highest risk of infection.

The distribution of schistosomiasis is extremely focal and since resources for health are seriously limited in most schistosomiasis endemic countries, there is a great need to identify high risk communities, so that resources can be better allocated. Due to the focal nature of the disease, neighbouring villages often show different patterns of schistosomiasis morbidity, resulting in large inter-village variation in perceived disease and actual public health importance. A simple procedure using questionnaires has been developed for rapid screening for *Schistosoma haematobium* infection and it proved to be reliable, non-intrusive and highly cost-effective in 8 African countries. Based on these experiences, WHO published guidelines for district health managers to be used as a first stage in the process of schistosomiasis control.

Côte d'Ivoire is now the first country, that has taken advantage of these guidelines and translated them into direct application. In a first step, the feasibility and diagnostic performance of the questionnaire was rigorously validated in an *S. haematobium* endemic area in central Côte d'Ivoire. Correctly completed questionnaires were obtained from 124 schools (return rate: 91%), with 12,479 children interviewed. Following, previously trained teachers screened 5,959 children with reagent sticks. The questionnaire showed a good diagnostic performance with sensitivity and specificity values between 79% and 96% to detect correctly those schools where the pupils were at high risk of infection. These findings were in agreement with previous studies from other African countries, and the questionnaire approach was recommended for use at the national level. At present, the questionnaires are already being applied in 5 out of 16 districts. The active involvement of University students in distributing and collecting questionnaires in this survey, is a promising innovative approach.

Based on the excellent performance of questionnaires for rapid screening of *S. haematobium* and linked to the ongoing process in Côte d'Ivoire, there was a demand asking for support with implementing this technique also in the Niger State of north-western Nigeria. Questionnaires were returned from 58 schools (return rate: 97%). A total of 3,033 children were interviewed and 2,479 children were screened with reagent sticks by previously trained teachers. Questionnaires also proved to be reliable in this setting, and identified schools at high risk of *S. haematobium* with sensitivity and specificity values ranging between 64% and 96%.

Summary

The identification of high risk communities is an important component in the management and implementation of cost-effective schistosomiasis control programmes. For *S. mansoni* infection, reliable rapid methods have not yet been developed. Therefore possible ways of extending the questionnaire method for *S. mansoni* were assessed in Côte d'Ivoire. In a first study, perceived signs and symptoms for intestinal morbidity were assessed in focus group discussions with schoolchildren in an area highly endemic for *S. mansoni*. The most frequently perceived signs and symptoms were then used in a preliminary questionnaire in three schools. Comparison of the results with levels of *S. mansoni* infection revealed that reported blood in stool was the most reliable symptom to predict an infection (adjusted odds ratio: 2.87; 95% confidence interval (CI): 1.56-5.31).

Based on these findings, a questionnaire was developed and distributed to 134 schools. Correctly filled-in questionnaires were returned from 121 schools (90%), with 12,227 children interviewed. 5,047 children were screened by a biomedical team with two consecutive Kato-Katz thick smears. For an individual diagnosis, the two symptoms "blood in stool" and "bloody diarrhoea" were significantly correlated with an *S. mansoni* infection: adjusted odds ratio 1.59 (95% CI: 1.38-1.83) and 1.34 (95% CI: 1.14-1.58), respectively. For community diagnosis, these two symptoms showed a high sensitivity (88%) and a moderate specificity (58%).

Subsequently, it was assessed whether the diagnostic performance of the questionnaire could be improved by asking questions about water contact patterns. Although a positive response to a particular water contact pattern correlated significantly with an infection with *S. mansoni*, the diagnostic performance was again only moderate. In view of these findings, it was concluded that there is still a considerable amount of research needed before questionnaires can be adopted as a tool to screen for *S. mansoni* at the community level.

Morbidity control in schistosomiasis requires effective initial treatment and the prevention of re-infection. In view of recent concern that praziquantel-tolerance/resistance might develop, there is a great need for research and development of novel substances with antischistosomal properties. Artemether has been identified in China as a promising product for early treatment and prophylaxis. It showed prophylactic effects in animals experimentally infected with *S. japonicum*, and was a successful prophylactic agent in humans exposed to *S. japonicum*. Further laboratory experiments showed a prophylactic effect also against *S. mansoni*. We conducted the first randomised double-blind placebo-controlled trial of oral artemether to prevent *S. mansoni* infections. 354 schoolchildren were enrolled. Stool samples were examined over four consecutive days, followed by two mass treatments with praziquantel four weeks apart. All *S. mansoni* negative children were randomly assigned to receive 6 repeated doses of a placebo (n=151) or artemether (n=138) at a dose of 6 mg/kg, spaced by 3 weeks. At the end of the study, the incidence and mean intensity of *S. mansoni* infection were assessed by examining four consecutive stool samples from the children. The group that received artemether had a significantly lower incidence of *S. mansoni* infection (31/128 vs. 68/140, relative risk: 0.50, 95% CI: 0.35-0.71, p<0.001). Furthermore, the geometric mean egg output among positive children in the artemether group (19 eggs/g stool) was significantly lower than

in placebo recipients (32 eggs/g, p=0.017). Oral artemether was found to be safe and no adverse events occurred. Since artemether is already widely and effectively used against malaria, the use of artemether against schistosomiasis should not be recommended for widespread application in areas where malaria is endemic because of the potential risk of developing drug resistance in the malaria parasite. However, the use of artemether might contribute to a more effective schistosomiasis control in particular epidemiological settings.

The findings of the present investigations clearly contributed to means of rapid identification of high risk areas of urinary and intestinal schistosomiasis in general and to the development and management of a national schistosomiasis control programme in Côte d'Ivoire in particular. We are optimistic that in the years to come considerable progress will be seen with the use of artemether (and hopefully also other drugs yet to be discovered) and that these products will take a promising place in a comprehensive strategy for schistosomiasis control.

Zusammenfassung

In den Tropen ist die Bilharziose nach der Malaria die am weitesten verbreitete parasitäre Infektionskrankheit des Menschen. Die Krankheit hat verheerenden Folgen für die betroffenen Bevölkerungsgruppen und die bestehenden Gesundheitssysteme und beeinflusst die sozio-ökonomische Entwicklung der betroffenen Regionen nachhaltig. Schätzungen gehen davon aus, dass 652 Millionen Menschen in Gebieten leben, wo sie sich jederzeit mit der Krankheit infizieren können, und dass rund 193 Millionen Menschen tatsächlich infiziert sind. Von den 120 Millionen geschätzten symptomatischen Fällen sind 20 Millionen Menschen schwer erkrankt. 85% dieser Fälle konzentrieren sich in afrikanischen Gebieten südlich der Sahara.

Seitdem sichere und effiziente Medikamente zur Verfügung stehen, wird die Kontrolle der Bilharziose hauptsächlich über die Bekämpfung der Krankheit selbst durchgeführt. Das Medikament der Wahl ist das preisgünstige Praziquantel, welches gegen alle Formen der Bilharziose hoch wirksam ist. Von zentraler Bedeutung für eine nachhaltige Krankheitskontrolle ist, dass das Medikament der Bevölkerung in Hochrisiko-Gebieten zugänglich gemacht werden muss.

Um die beschränkten finanziellen Mittel in Entwicklungsländern optimal zu nutzen, ist es wichtig, die Risikogebiete richtig zu lokalisieren. Es ist bekannt, dass selbst zwischen Nachbardörfern eine ganz unterschiedliche Anzahl Krankheitsfälle beobachtet werden kann, was dazu führt, dass die Bedeutung der Krankheit grossen interkommunalen Schwankungen unterliegt. Bei der Blasenbilharziose konnte eindrucksvoll aufgezeigt werden, dass einfache Fragebogen ein kostengünstiges und verlässliches Mittel sind, um Dörfer korrekt zu lokalisieren, wo die Krankheit ein grosses Problem darstellt. Diese Methode wurde bis anhin in 8 verschiedenen afrikanischen Ländern erfolgreich angewandt. Auf diesen positiven Erfahrungen basierend hat die Weltgesundheitsorganisation konzise Richtlinien zusammengestellt, die direkt von den lokalen Gesundheitsbehörden benutzt werden können, als erster Schritt für die Konzeptionierung eines Kontrollprogrammes.

Die Côte d'Ivoire ist nun das erste Land, welches mittels dieser Richtlinien einen wichtigen Schritt in Richtung Bilharziose Kontrolle gegangen ist. Als erstes wurde die Akzeptanz und die Genauigkeit dieser Methode getestet und zwar im Zentrum der Côte d'Ivoire, wo Blasenbilharziose weit verbreitet ist. Fragebögen wurden in 124 Schulen korrekt ausgefüllt und insgesamt wurden 12'479 Kinder interviewt. Danach wendeten Lehrer einen einfachen diagnostischen Test an, und überprüften bei insgesamt 5'959 Schulkindern, ob sie mit Blasenbilharziose infiziert waren. Wie bereits in früheren Studien gezeigt werden konnte, war der Fragebogen ein verlässliches Mittel, um die Schulen herauszufinden, wo Blasenbilharziose am häufigsten vorkam (Sensitivität und Spezifizität: 79-96%). Aufgrund dieser Resultate wurde die Methode für das nationale Kontrollprogramm vorgeschlagen und kam unmittelbar danach zur grossflächigen Anwendung. Bis anhin wurde die Methode in 5 der 16 Distrikte angewandt, wobei ein innovativer Ansatz getestet wurde, mit Integration der Universität.

Zusammenfassung

Als wie wir die Methode an der Côte d'Ivoire austesteten, wurden wir von Gesundheits-Verantwortlichen im Niger Distrikt im Nordwesten von Nigeria angefragt, ob wir ihnen helfen könnten, die Methode auch dort zu evaluieren. Fragebogen kamen in 58 Schulen zur Anwendung und 3'033 Kinder wurden befragt. Die Lehrer untersuchten anschliessend 2'479 dieser Kinder mit einem einfachen Test, ob sie die Blasenbilharziose haben. Auch in dieser Studie erwiesen sich die Fragebögen als verlässlich, um diejenigen Schulen zu identifizieren, wo Blasenbilharziose ein zentrales Problem darstellt (Sensitivität und Spezifizität: 64-96%).

Für eine kostengünstige Kontrolle der Bilharziose ist eine zuverlässliche Identifikation von Hochrisiko-Gebieten von grosser Bedeutung. Für die Dickdarmbilharziose stehen solche Methoden noch nicht zur Verfügung. Aus diesem Grund haben wir versucht, einen analogen Fragebogen zu entwickeln, welcher erlauben würde, die Hochrisiko-Gebiete zu lokalisieren. Eine Serie von Studien wurde im Westen der Côte d'Ivoire lanciert, einem Gebiet, wo die Dickdarmbilharziose stark verbreitet ist. In der ersten Studie wurden Zielgruppen-Diskussionen mit Schulkindern durchgeführt. Die Kinder sollten Auskunft geben über ihre gängigsten Symptome bezüglich Unterleibserkrankungen. Diese Symptome wurden dann in einen ersten Fragebogen integriert und dieser wurde in der Folge an drei Schulen evaluiert. Ein Vergleich der Antworten und der Laborresultate zeigte, dass das Symptom "Blut im Stuhl" die verlässlichste Antwort war, um eine Dickdarmbilharziose richtig vorherzusagen (korrigierte Odds Ratio: 2.87; 95% Konfidenz-Intevall: 1.56-5.31).

An Hand dieser Ergebnisse wurde ein zweiter Fragebogen entwickelt und an 134 Schulen verteilt. 121 Schulen führten die Befragungen durch und interviewten 12'227 Kinder. Unsere Forschungs-Equippe untersuchte Stuhlproben von zwei aufeinanderfolgenden Tage von insgesamt 5'047 Kindern (Kato-Katz Methode). Zwei Symptome, "Blut im Stuhl" und "blutiger Durchfall" korrelierten signifikant mit einer Dickdarmbilharziose-Infektion. Die beiden korrigierten Odds Ratios waren wie folgt: 1.59 (95% Konfidenz-Intervall:1.38-1.83) und 1.34 (1.14-1.58). Diese beiden Symptome resultierten in einer hohen Sensitivität (88%) jedoch lediglich in einer moderaten Spezifität (58%), um eine Schule korrekt als Hochrisiko-Gebiet der Dickdarmbilharziose einzustufen.

In einer dritten Studie wurde untersucht, ob die Fragebogen-Methode durch ergänzende Fragen über typische Wasserkontakte verbessert werden könnte. Obwohl einige Fragen signifikant mit einer Dickdarmbilharziose-Infektion korrelierten, waren die Sensitivität und die Spezifizität erneut nur moderat. Es wurde abschliessend festgehalten, dass weitere zusätzliche Studien nötig seien, bevor Fragebogen zur weitflächigen Anwendung kommen, für die Identifikation von Hochrisiko-Gebiete der Dickdarmbilharziose.

Für eine nachhaltige Krankheitskontrolle der Bilharziose ist eine effiziente Erstbehandlung nötig, sowie die Verhinderung von Reinfektionen. In Anbetracht der befürchteten Resistenzen gegenüber Praziquantel ist die Erforschung und Entwicklung alternativer Medikamente von grosser Bedeutung. Bedeutende Resultate wurden neulich in China erzielt, wo Artemether sowohl in Tierversuchen als auch in klinischen Studien eine starke prophylaktische Wirkung

gegenüber einer asiatischen Form der Bilharziose zeigte. Eine Serie von Laborexperimenten konnte die prophylaktische Wirkung von Artemether auch gegen die Dickdarmbilharziose Parasiten bestätigen. Auf Grund dieser Ergebnisse wurde an der Côte d'Ivoire die erste Placebo-kontrollierte Doppelblindstudie durchgeführt. Die Studie wurde mit 354 Schulkinder durchgeführt. Zuerst wurde während vier aufeinanderfolgenden Tage untersucht, welches Kind mit dem Parasiten infiziert war. Alle Kinder wurden dann innerhalb von vier Wochen zweimal mit Praziquantel behandelt. Diejenigen Kinder die nach der zweiten Behandlung keine Parasiten mehr aufwiesen, wurden zufälligerweise mit einem Placebo (n=151) oder mit Artemether (6 mg/kg) behandelt (n=138). Sechs Behandlungen wurden durchgeführt, einmal alle drei Wochen. Am Ende der Studie wurde evaluiert, wie viele Kinder sich neu infiziert hatten und wie stark die Infektions-Intensität bei diesen positiven Kindern war. Unsere Resultate zeigten klar auf, dass Behandlungen mit Artemether sicher sind, und dass die Anzahl Neuinfektionen in der Artemether-Gruppe (31/128) signifikant tiefer war als in der Placebo-Gruppe (68/140). Das relative Risiko einer Neuinfetion konnte um 50% (95% Konfidenz-Intervall: 35-71%) reduziert werden. Zusätzlich stellten wir fest, dass die Infektions-Intensitäten in der Artemether-Gruppe (19 Parasiten-Eier pro Gramm Stuhl) signifikant tiefer war als in der Placebo-Gruppe (32 Eier).

Zur Zeit wird Artemether bereits weitflächig und mit grossem Erfolg gegen Malaria eingesetzt. Sollte Artemether über einen langen Zeitraum und grossflächig zur Anwendung kommen, so besteht rein theoretisch die Gefahr, dass die Malaria-Parasiten eine Resistenz entwickeln könnten. Bevor nicht weitere Forschungsresultate vorliegen, sollte Artemether momentan nicht in Gebieten angewendet werden, wo sowohl die Dickdarmbilharziose wie auch die Malaria endemisch sind.

Die Resultate der hier vorliegenden Doktorarbeit tragen zweifelsohne dazu bei, dass in Zukunft Hochrisiko-Gebiete der Blasen- und der Dickdarmbilharziose effizienter angegangen werden können. Für das nationale Kontrollprogramm an der Côte d'Ivoire sind wichtige Schritte im Gange, um die Bekämpfung der Krankheit besser in den Griff zu bekommen. Wir sind zuversichtlich, dass Artemether (und hoffentlich auch weitere noch zu entdeckende Medikamente) eine wichtige Position einnehmen werden, um die Bilharziose in Zukunft mit einer umfassenden Strategie bekämpfen zu können.

1 Introduction

1.1 The global burden of human schistosomiasis

Human schistosomiasis is an important and widespread infection in the tropics. It gives rise to a complex of acute and chronic diseases with widely differing signs and symptoms (WHO 1993). It is the second most prevalent parasitic disease after malaria in the developing world with a huge impact on public health and socio-economic development (Doumenge *et al.* 1987, WHO 1993, 1998). Based on the latest extrapolations it is estimated that 652 million people live at risk of infection and that 193 million people are actually infected with schistosomiasis, of whom 85% are concentrated in sub-Saharan Africa (WHO 1999). It is believed that there are 120 million symptomatic cases, of whom 20 million are suffering from severe disease (WHO 1999). Recently, the concept of disability-adjusted life years (DALY) was developed in order to assess and refine estimates of the global burden of disease (World Bank 1993). For sub-Saharan Africa, a morbidity burden due to schistosomiasis of 3.5 million DALYs has been estimated. In comparison with all other communicable diseases, schistosomiasis therefore ranks in position ten, after respiratory infections (31.6 million DALYs), malaria (31.5), diarrhoeal diseases (30.4), HIV infections (18.4), measles (16.1), tuberculosis (13.7), sexually transmitted diseases excluding HIV (7.5), tetanus (5.8) and pertussis (4.8), as reviewed by Murray *et al.* (1994).

Although these numbers have to be cited with caution, as they were calculated after extrapolation of (often limited) prevalence survey data and were aggregated to country level, they clearly indicate the tremendous public health significance of schistosomiasis. Although several investigations have been performed to estimate the direct impact of infection with schistosomiasis on the school performance of children, their physical fitness and productivity, the results are inconclusive. Some studies revealed a clear negative impact due to an infection with schistosomiasis, while others did not (Gryseels 1989, Tanner 1989). This discrepancy was explained by the difficulty of devising a standardized methodology, and by other confounding factors, for example concurrent infection with another disease (Tanner 1989). The recent advance in methods of calculating attributable risk allows the fraction of a particular morbidity indicator which was attributable to an infection with schistosomiasis to be calculated (Guyatt *et al.* 1995a, Booth 1998).

There is general agreement that the global prevalence of schistosomiasis will most likely increase due to the following three reasons: (1) increasing numbers of irrigation systems for agriculture and cattle breeding, (2) constructions of dams and man-made lakes for hydroelectric power production and (3) civil strife and war which contribute to additional human migration (Mott *et al.* 1995).

Despite the tremendous global burden of schistosomiasis, and the likelihood of the disease gaining importance, its public health significance is often underestimated. There are two common explanations for this: (1) schistosomiasis is focally distributed and (2) severe disease only follows after many years of mildly symptomatic infections (Homeida *et al.* 1988, WHO

1993). In most African countries, where resources are very limited and need to be allocated in the most effective way, primary health care delivery systems have to deal with many other and often more visible health problems, such as malaria and HIV (Gryseels 1989, Gryseels & Polderman 1991). These reasons also explain why schistosomiasis control is often given a low priority and that many endemic countries have never set up national control programmes (Kusel & Hagan 1999). However, the prospects of controlling schistosomiasis are good, as health managers have now sensitive but inexpensive diagnostic tools, and most importantly a safe, effective and cheap drug at their disposal (Kusel & Hagan 1999).

1.2   The parasite and its life cycle

Schistosomiasis is caused by an infection with fluke worms (Trematoda, Platyhelminths) of the family Schistosomatidae, belonging to the genus *Schistosoma*. There are five species that are able to infect man: *Schistosoma haematobium*, *S. intercalatum*, *S. mansoni*, *S. japonicum* and *S. mekongi*. These species can be subdivided into three groups characterized by the size, shape and appearance of the eggs produced by the female worm: (1) *S. haematobium* and *S. intercalatum* produce ovoid eggs with a size of 60x140-170 mm and a terminal spine, (2) eggs of *S. mansoni* have a similar shape and size but a lateral spine, and (3) *S. japonicum* and *S. mekongi* produce smaller eggs (size: 50-90 mm) that are rounded and have only a rudimentary spine (WHO 1994, Davis 1996).

The two species considered in the present thesis are *S. mansoni* and *S. haematobium*. Currently, *S. mansoni* is endemic in 55 countries mainly in sub-Saharan Africa, including the Arabian peninsula, Egypt, Libya and Sudan, but also in some countries and territories of South America (Brazil, Venezuela, Surinam and some Caribbean islands). *S. haematobium* is currently found in 53 countries in the Middle East and most of the African continent including the islands of Madagascar and Mauritius (WHO 1999). Most of the results that will be presented in the following chapters were obtained in a series of field studies carried out in Côte d'Ivoire (West Africa), a country where both *S. mansoni* and *S. haematobium* are endemic.

The life cycle of schistosomiasis is complex. It involves a phase of sexual reproduction by adult schistosomes in the definitive human host, an asexual phase in the intermediate host, a freshwater snail. From the snail, cercariae are released into the surrounding water and can invade humans through the skin (Figure 1.1).
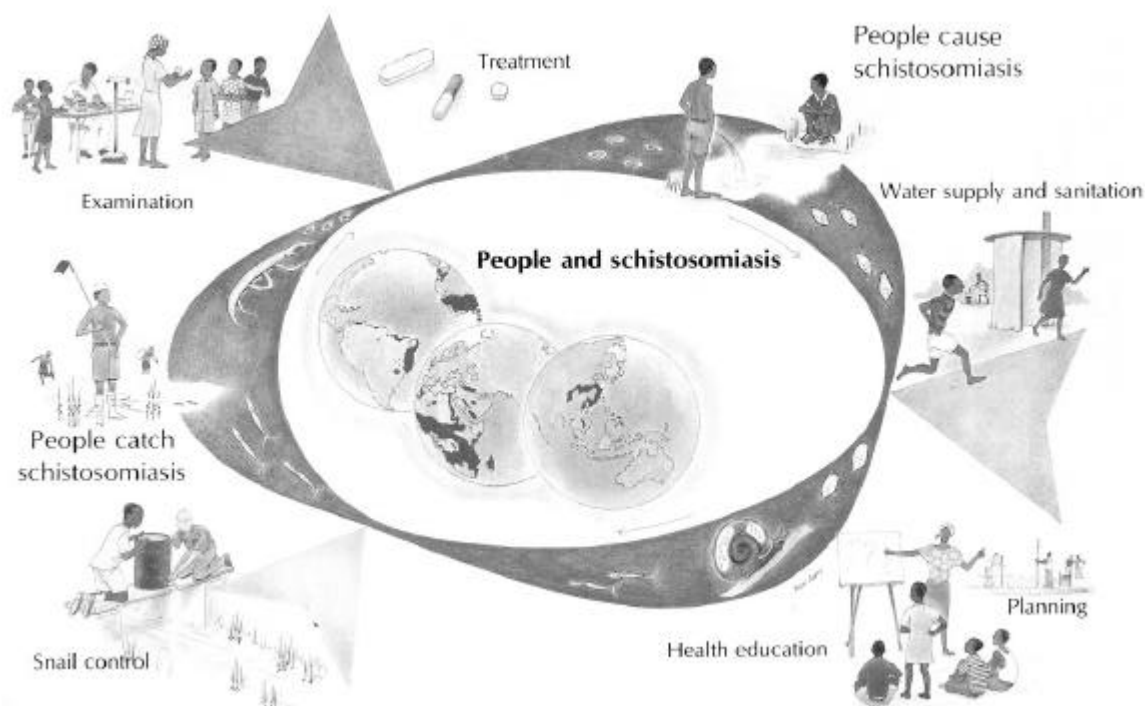
Figure 1.1
Life cycle of schistosomiasis and potential control strategies (WHO 1990).

Adult schistosomes are small white-grey worms varying in length from 6-26 mm and in width from 0.2-1.1 mm, depending on species and sex. The sexes are separate. The female worm is slender, and is longer than the male. They live in couples with the female permanently held by the male in a longitudinal 'schist' or gynaecophoric canal (Sturrock 1993). Worm couples of the species *S. mansoni* inhabit the pericolonic venules within the portal venous system and *S. haematobium* worm pairs inhabit the terminal venules in the wall of the bladder, the genitourinary system and the pelvic plexus within the distribution of the inferior vena cava of the definitive human host (Davis 1996). Here, the worms feed on blood. It has been estimated that the average life span of *S. mansoni* worms is 3.3 years (Goddard & Jordan 1980) and that of *S. haematobium* is 3.4 years (Wilkins *et al*. 1984), but there is a confirmed report of viable *S. mansoni* eggs being discovered 37 years after a subject had left the endemic area (Chabasse *et al*. 1985).

An adult *S. mansoni* female worm produces 100-300 eggs per day, and *S. haematobium* produces 20-300 eggs per adult female per day (Sturrock 1993). It is assumed that approximately 50% of the eggs pass through the colon, the walls of the bladder or the genitourinary apparatus and are excreted by faeces or urine. The remaining 50% of the eggs are trapped within the tissues of these organs (Davis 1996). In infections with *S. haematobium*, these eggs give rise to inflammation, haemorrhages and pseudopolyposis. Inflammation and in later stages calcification of the eggs can lead to stasis, hydroureter, hydronephrosis, kidney failure and even bladder carcinoma. In infections with *S. mansoni*, some of the eggs are

trapped in the intestinal wall and lead to inflammation and pseudopolyposis, which may result in abdominal pain and blood in the faeces. Other eggs are carried away and are finally trapped in the portal system of the liver and may cause hepatosplenomegaly. In a later stage these lesions may become fibrous, this condition is called "Symmer's pipe-stem fibrosis".

Excreted eggs hatch after they have come into contact with a suitable aquatic environment, and they release a miracidium, which swims actively and is able to locate – most likely by chemotaxis – a compatible freshwater snail. Interestingly, there are only very few snail species that are compatible and these are schistosome species-specific. In Côte d'Ivoire, *Biomphalaria pfeifferi* is the only intermediate snail host for *S. mansoni* (N'Goran *et al*. 1989), whereas both *Bulinus globosus* and *B. truncatus* act as intermediate snail hosts for transmission of *S. haematobium* (N'Goran *et al*. 1997a).

Miracidia penetrate into the intermediate snail host, predominantly via the foot of the snail (Jourdane & Théron 1987). After penetration and close to the entry point, a small proportion of both male and female miracidia develop into mother sporocysts. They might produce daughter sporocysts which migrate to other parts of the snail body. Subsequently, there is an asexual multiplication within the mother and the daughter sporocysts and each forms many thousand cercariae, all of the same sex. According to biological, environmental and physical determinants, it takes between 4 and 6 weeks from the penetration of a miracidium to the production of mature cercariae (Webbe 1982). Furthermore, the production of cercariae fluctuates daily and, in general, decreases with the age of the intermediate snail host. This was confirmed during recent laboratory experiments with *S. haematobium*-infected *B. globosus* snails collected from central Côte d'Ivoire and conditioned in the laboratory of the Swiss Tropical Institute (Yvette Endriss & Jacques Chollet, personal communication).

When cercariae emerge from the snails, they are directly released into the freshwater environment. It is suggested that the main stimulus for their release is light intensity; therefore emergence follows a circadian rhythm. Recently, the cercarial shedding patterns of *S. haematobium* were analysed in Côte d'Ivoire along a North-South transect. Peak intensity was observed around noon. However, the mean shedding time in the forest zone in the South (11:00 hours) was significantly earlier than the one in the savannah zones in the North (13:40 hours) (N'Goran *et al*. 1997a).

Cercariae are non-feeding organisms and they have a relatively short life span of between 36 and 48 hours. If they find a human host within this time, they are able to penetrate the skin while the human is in contact with the infested water during occupational and/or recreational activities. It is remarkable that the process of penetration only takes a few minutes and is coupled with the transition of the cercaria from a freshwater to a saltwater (isotonic) environment in the human body. After penetration, the cercariae lose their tails and are subsequently called schistosomula. They traverse the subcutaneous tissue within 2 days and penetrate into the venous or lymphatic channels, when they are transported to the right side of the heart and lungs. Then, schistosomula leave the lungs and are distributed passively with the

blood flow to the systemic organs. Most of the parasites are trapped in the liver. Sexual maturity is reached in the liver with a schistosome-species specific duration. For *S. mansoni*, it takes between 25 and 30 days (Clegg 1965). For *S. haematobium*, sexual maturation is reached at day 31, however the pre-patent period is much longer, approximately 70 days (Smith *et al*. 1976). During the development from schistosomula to adult worm a feverish syndrome called "Katayama fever" may develop, usually in previously non-exposed individuals. After the worms have paired, they remain attached together and actively migrate against the blood flow in the hepatic portal vein to finally inhabiting the two venous branches around the intestine (*S. mansoni*) or the vesicul plexus (*S. haematobium*). In these locations, they begin to lay eggs, which are detected in faeces and urine, respectively, some 6 to 10 days later.

1.3 The epidemiology of human schistosomiasis

For a comprehensive understanding of the epidemiology of human schistosomiasis five features of the disease are of central importance: (1) it is complicated, (2) it is heterogeneous in time, (3) it is heterogeneous in space, (4) it shows aggregation and (5) is sensitive to environmental alterations.

(1) Complicated epidemiology

As outlined in the previous chapter, the epidemiology of schistosomiasis involves humans as the definitive host, various but very specific aquatic or amphibious snails acting as intermediate hosts, and freshwater as the environment where the disease is transmitted. However, transmission only occurs when schistosome eggs reach the freshwater environment, as a result of the absence of appropriate sanitary facilities, or insanitary behaviour of humans, directly contaminating the freshwater environment with their excreta. Humans can then acquire the disease by (repeated) contact with the infested water, by means of recreational and/or occupational activities (Davis 1996).

(2) Heterogeneity in time

In most, if not all areas where it is endemic, schistosomiasis is characterised by seasonal transmission patterns. In numerous studies it has been shown that the distribution and density of the intermediate snail host is an important determinant, accounting to a large extent for the observed variability in rates of schistosomiasis infection (Babiker *et al*. 1985, Woolhouse & Chandiwana 1989, 1990a, b, Woolhouse 1992). There is firm evidence that in lotic environments, water current velocity is the key determinant influencing the distribution of snails, and that in lentic environments, water temperature plays the key role for snail abundance (Appleton 1978). Both water current velocity and temperature vary over time and show a seasonal pattern, therefore are the most important factors explaining the heterogeneity of epidemiological patterns in time.

(3)   Heterogeneity in space

It is widely accepted that schistosomiasis has a focal distribution (e.g. Webbe & Jordan 1993, WHO 1993). It is assumed that the focal nature of the disease is the result of the complex interrelationship between the distribution and the density of infected persons and of compatible intermediate snail hosts, the distance between infected persons and suitable freshwater environments that are contaminated and act as transmission sites, and the frequency and duration of water contacts of humans. The focality of schistosomiasis is well documented world-wide, with the disease currently being endemic in 76 countries and territories over several continents (WHO 1999). The spatial heterogeneity is also well illustrated within countries, with specific foci of schistosomiasis being restricted to only those areas where all components of the schistosomiasis complex also converge in time (e.g. Doumenge *et al*. 1987). Focal distribution on a regional scale has been observed in many studies (e.g. Hunter *et al*. 1993, Red Urine Study Group 1995, Malone *et al*. 1997). However, the microgeographical distribution of schistosomiasis within a community has received far less attention because its complexity requires more detailed assessment. Nonetheless, it has been shown convincingly that the mean frequency and the mean duration of water contacts per person, as well as the mean number of sites frequented per person, correlate with the intensity of intestinal schistosomiasis (Kloos *et al*. 1997) and urinary schistosomiasis (Useh & Ejezie 1999). The distribution of intermediate snail hosts has been studied, and preferences for particular habitats and specific habitat features could be shown (Thomas & Tait 1984, Ndifon & Ukoli 1989, Woolhouse & Chandiwana 1989, Odermatt 1994). In a recent study attention was drawn to the microhabitat level, by showing that snails showed spatial microhabitat preferences within a single river system (Utzinger *et al*. 1997).

(4)   Aggregation

It is well established that the prevalence and intensity of schistosome infections both peak in specific age groups (Woolhouse 1998). The likely explanation for this pattern is the fact that these age-groups are most frequently exposed to schistosome-infested water. It is also widely acknowledged that the distribution of schistosome worm pairs per person is extremely uneven, resulting in a great variation in the number of excreted eggs per person. The majority of the population only excrete a few schistosome eggs, while a small proportion of people are responsible for the greater part of the egg excretion (Bradley 1972, Polderman 1979, Anderson & May 1985, Guyatt *et al*. 1995b). Furthermore, there is individual day-to-day variation in schistosome egg output, which was comprehensively reviewed by Hall (1982). There is also intra-stool variation in the number of schistosome eggs, but this is less important than the day-to-day variation (Engels *et al*. 1997). The aggregation of worms in individual human hosts is of considerable importance for understanding the transmission dynamics of schistosomiasis, and ultimately for the control of the disease.

(5)   Dynamic epidemiology

Areas confirmed to be free of schistosomiasis at a particular point in time can rapidly become important disease foci and may challenge previously unexposed populations. Often, environmental alterations, for example caused by water resource development projects (damming and irrigation), are the cause of an onset of schistosomiasis transmission (e.g. Wen & Chu 1984, Hunter *et al*. 1993). There is accumulated evidence from several countries that the completion of dam constructions may also be followed by a changing pattern of schistosomiasis with a shift in predominance from urinary to intestinal schistosomiasis (Abdel-Wahab *et al*. 1979, Mott *et al*. 1995). The latest example is reported from Senegal, where an outbreak of intestinal schistosomiasis was observed only three years after the completion of the Diama dam (Talla *et al*. 1990, Picquet *et al*. 1996, Southgate 1997). However, though the construction of two large dams in Côte d'Ivoire was followed by a significant increase in the prevalence of *S. haematobium*, *S. mansoni* remained at a very low prevalence, therefore no shift was observed so far (N'Goran *et al*. 1997b). It is interesting to note that in the Kilombero district in Tanzania *S. haematobium* was the predominant schistosome species for many years (Zumstein 1983), but recent studies suggest that *S. mansoni* is spreading rapidly (Odermatt 1994, Pervilhac *et al*. 1998) and will eventually replace *S. haematobium*.

1.4   Diagnosis of human schistosomiasis

Diagnosis is of pivotal importance for all aspects of human schistosomiasis (Feldmeier 1993). The decision to treat an individual with an antischistosomal drug, the assessment of morbidity due to schistosomiasis, the rapid identification of communities at highest risk of infection, studies of the regression and reappearance of pathology after chemotherapy, or the evaluation and monitoring of control programmes, are all based on the results of diagnostic tests. There are many different techniques and approaches that may be used both at the individual and community level. Their selection and application depends not only on the type of information sought but also the resources available. From a public health perspective, simple and robust techniques are requested, which and can be performed with supplies and equipment that are readily available (WHO 1993). In addition, they should be inexpensive and easily applicable in the field (WHO 1999).

The diagnostic techniques that were used in the study descibed here were urine filtration and Kato-Katz thick smears. They are discussed in detail below. Both methods are used to directly demonstrate the presence of schistosome eggs in urine and faeces, respectively. They are the most commonly used techniques in epidemiological surveys (WHO 1999). Indirect methods also exist, which rely on perceived symptoms, clinical examinations, or biochemical or immunological disease markers. The use of perceived symptoms for rapid screeing of

S. haematobium and *S. mansoni* and the use of reagent sticks for the detection of microhaematuria (biochemical marker for *S. haematobium*) were also used in the present study and are discussed below.

It is interesting to note that over the last 10 years remarkable progress has been made with immunological disease markers (WHO 1999). The existence of detectable amounts of circulating antigens (circulating anodic antigen and circulating cathodic antigen) in schistosome-infected people has prompted research into their potential for immunodiagnosis. Subsequently, a variety of assay methods has been developed (Deelder *et al*. 1989, De Jonge *et al*. 1989, Gunderson *et al*. 1992, Van Lieshout *et al*. 1995a, b, Van Etten *et al*. 1997). Schistosome infections can also be indirectly detected by the presence of antibodies (for review see Hamilton *et al*. 1998).

Diagnosis using imaging techniques to detect pathology due to schistosomiasis has also been increasingly used over the last 15 years. With the exception of ultrasound, these rather sophisticated techniques are performed in hospital settings. The advent of portable ultrasound devices allowed the technique to be carried into the field. The first experience was reported by Degrémont *et al*. (1985). This safe and non-invasive method has since proved to be feasible, relatively rapid for assessing pathology resulting from schistosome infections in surveys (Hatz *et al*. 1992a, b). It proved to be especially useful in investigating the resolution (Hatz *et al*. 1990) and reappearance of pathology following treatment (Hatz *et al*. 1998, Wagatsuma *et al*. 1999).

(1)   Urine filtration

Usually 10 ml of urine is filtered through a membrane (consisting of paper, polyamide (Nytrel) or polycarbon). Depending on the filter material, the membrane needs to be stained with one or two drops of a coloring solution (Nile-blue, lugol, eosin, hematoxylin or carbofuchsin). Then the membrane is scanned under a light microscope. The use of Nytrel filters (Plouvier *et al*. 1975) has been recommended for large-scale community-based schistosomiasis control programmes, as their cost is low and they can be re-used (Mott 1982, WHO 1985). However, in subsequent studies it was reported that a significant proportion of filters retained *S. haematobium* eggs even after thorough washing, which led to false-positive results (Rohde *et al*. 1985, Klumpp & Southgate 1986). Although this was questioned by Mott (1988), alternative washing procedures were evaluated and boiling of filters for at least 5 minutes in tap water prior to washing was found to be a reliable method to remove all eggs, so that filters could be re-used (Mshinda *et al*. 1989). Many years ago, it was established that the excretion of *S. haematobium* eggs follows a circadian rhythm, with a peak and the lowest variability being observed around noon (Bradley 1963). Therefore urine specimens should be collected between 10 am and 2 pm. Infected individuals are classified as having light (< 50 eggs/10 ml of urine) or heavy (≥ 50 eggs/10 ml of urine) infections (WHO 1993).

(2)   Kato-Katz thick smear

In the mid 1950s, Kato & Miura (1954) introduced the idea of faecal thick-smear examinations. The use of glycerol for the clearing of faecal material was described, which allowed to analyse larger stool samples than before. Some 20 years later, Katz and collaborators described a modification of this initial method for the quantification of *S. mansoni* eggs in stool (Katz *et al*. 1972). It has since become the most widely used technique for the diagnosis of *S. mansoni* (WHO 1999) and is also used in studies with *S. japonicum* (Yu *et al*. 1998) and *S. mekongi* (Stich *et al*. 1999). The procedure is relatively simple and can be summarized as follows: a small amount of fresh stool is sieved through a fine screen and filled into a hole of defined dimensions in a plastic template of standard thickness, placed on the centre of a microscope slide. This provides a stool sample of known volume. After carefully removing the template, the faecal material is covered with a strip of cellophane, previously soaked in glycerol and malachite green. The microscope slide is inverted and firmly pressed against a hard surface, so that the faecal material is evenly spread. After clarification (time depending on the amount of faeces), the slide can be scanned under a microscope at low magnification (WHO 1994). With the templates used by Katz *et al*. (1972), the measured amount of stool is approximately 43.7 mg. Subsequently, modifications were proposed with the aim of simplifying the preparation. These included using a thick glass cover slip instead of the cellophane (Teesdale & Amin 1976) and reducing the clearing time by using templates giving only 20 mg samples (Peters *et al*. 1980). At present, different commercial kits are on the market, most commonly with 43.7 mg or 25 mg slides (Polderman *et al*. 1985). Egg counts can easily be converted into eggs per gram of stool (epg) by multiplication by a factor of 24 or 40, respectively. According to the WHO classification (1993), there are three intensity levels: (1) light infection: 1-100 epg, (2) moderate infection: 101-400 epg, and (3) heavy infection: > 400 epg. In population surveys, the geometric mean egg output is also frequently calculated and often used for the evaluation and monitoring of control programmes.

These two direct parasitological techniques – urine filtration and Kato-Katz thick smears – are considered 'gold standards' for diagnosis, especially when repeated specimens are analysed, and the results obtained by alternative techniques are tested against them. The main advantages of both methods are their very high specificities, approaching 100%, their relative ease in execution, their direct applicability in the field and the fact that they provide quantitative results. In addition, faecal thick smears also allow the identification and quantification of concurrent helminth infections, such as hookworms, *Ascaris lumbricoides*, *Trichuris trichiura* and *Taenia* sp.

Like all other diagnostic techniques, both urine filtration and Kato-Katz thick smears have also limitations. Firstly, the collection of specimens is tedious and may not be well accepted in certain cultures (especially the collection of stool). Secondly, only a very small amount of excreta is analysed. Thirdly, there is intra-specimen variation in egg counts (Engels *et al*. 1997), and even more importantly, day-to-day variation in egg-output (Engels *et al*. 1996a).

bTherefore, analysis of a single specimen fails to estimate the true proportion of infected individuals, with light infections most likely to be missed (De Vlas & Gryseels 1992, De Vlas *et al*. 1992, 1993, 1997). When emphasis is placed on individual diagnosis, analysis of several stool specimens over consecutive days is recommended (De Vlas & Gryseels 1992, Engels *et al*. 1996a). However, it is well acknowledged that such procedures fatigue study subjects, resulting in low compliance (WHO 1999).

Besides urine filtration and Kato-Katz thick smears, there are some alternative approaches for the direct parasitological demonstration of eggs in excreta. The more traditional diagnosis of *S. haematobium* was urine centrifugation/sedimentation. Although the method has a high sensitivity, which is even superior to that of filtration of 10 ml urine samples in low intensity infections (Richards *et al*. 1984), it is not suitable for large-scale community screening because it is too labor-intensive and requires well-equipped laboratories.

Direct faecal smears are an alternative to Kato-Katz thick smears. The method is widely used in health facilities; smears are very easy to prepare and the slides can be read immediately under a microscope. Unfortunately, the amount of stool analysed with a direct faecal smear is 10-20 times smaller than with a Kato-Katz thick smears and therefore the sensitivity for detection of *S. mansoni* eggs is considerably lower (Engels *et al*. 1996b). It is often important to look for concurrent infections. Direct faecal smears are a good means to detect hookworm eggs.

Finally, there exist also some rather sophisticated concentration techniques. They are mainly used in specialized laboratories with skilled personnel. The sodium acetate-acetic acid-formalin method has a relatively low sensitivity for *S. mansoni* and geohelminths, but is reliable for diagnosing intestinal protozoa, such as amoebiasis and giardiasis (Marti & Escher 1990).

(3) Perceived disease markers

Over the last decade there has been a considerable amount of research on perceived morbidity indicators of schistosomiasis, with the aim of developing a procedure that would allow the rapid identification of communities at high risk of schistosomiasis (WHO 1999). Excellent progress has been made with rapid screening of *S. haematobium* using simple questionnaires administered through schools. Based on these results, it was hoped that a similar questionnaire procedure might also be developed for *S. mansoni*.

Questionnaires for S. haematobium

Although blood in urine (haematuria) has been associated with *S. haematobium* for a very long time, it was only 15 years ago when Mott *et al*. (1985) assessed the usefulness of asking children in Ghana and Zambia about the presence of blood in urine as an indirect diagnosis of infection. However interviewer bias, and considerable variation in results between the two epidemiological settings raised concern about the reliability of this approach. Four years later a comprehensive school-questionnaire was presented for the first time which allowed the rapid identification of high risk communities for *S. haematobium* in a rural district in Tanzania (Lengeler 1989, Lengeler *et al*. 1991a). The idea of asking schoolchildren about the presence of blood in urine was also used on Pemba Island, and it was found that this question was a sensitive indicator for heavily infected boys (Savioli *et al*. 1989). Consequently, the method was validated with success in a neighbouring district (Lengeler *et al*. 1991b), and also in seven other African countries in the frameworkd of a WHO/TDR-supported multi-country study in Cameroon, Congo, Democratic Republic of Congo (formerly Zaïre), Ethiopia, Malawi, Zambia and Zimbabwe (Red Urine Study Group 1995). So far, with only one exception, Ethiopia (Jemaneh *et al*. 1996), highly significant correlations were found between the proportion of children reporting blood in urine, and the proportion of *S. haematobium* infected children.

It was concluded that school-questionnaires provide rapid and reliable results, are non-intrusive and highly cost-effective in the screening of *S. haematobium* at the community level. However, it was pointed out that further validation is mandatory, when significant changes have been made to the questionnaire or where strong arguments are required to convince health authorities about the usefulness of this method for a particular place (Chitsulo *et al*. 1995).

In the case of Côte d'Ivoire, both these reasons applied. When the original questionnaire (Lengeler *et al*. 1991a, b) was presented to health authorities and school teachers, it was felt that it needed considerable modification before application on a larger scale. Furthermore, the national co-ordinator for schistosomiasis control was interested in using questionnaires as a first step of the programme to identify priority areas, and a thorough validation of questionnaires was therefore requested to provide a solid foundation for later application on a national scale.

Questionnaires for S. mansoni

There has been considerable discussion about the development of a similar questionnaire method for rapid identification of individuals and/or communities at highest risk of *S. mansoni*. It is widely acknowledged that this is a complex issue, because the signs and symptoms associated with infection and/or morbidity generally show low sensitivities and specificities.

Several hospital- and community-based studies have been conducted to assess the morbidity due to *S. mansoni*. They also provided information on the diagnostic value of signs and symptoms associated with infection an of *S. mansoni*. These studies clearly revealed significant associations between an infection with *S. mansoni* and the presence of diarrhoea (especially bloody diarrhoea) and/or blood in the stool for most areas of sub-Sahara Africa (Arap Siongok *et al*. 1976, Hiatt 1976, Omer *et al*. 1976, Hiatt & Gebre-Medhin 1977, Abdel-Wahab *et al*. 1980, Sukwa *et al*. 1985, Sukwa *et al*. 1986, Gryseels & Poldermann 1987, Gryseels 1988, Gryseels & Nkulikyinka 1990, Gryseels & Poldermann 1991, Kardorff *et al*. 1997). In addition to blood in stool and (bloody) diarrhoea, abdominal pain and colicky cramps were correlated with an *S. mansoni* infection (Gryseels 1992).

However, another study in Zambia could not demonstrate any association between any one of the above symptoms and an infection with *S. mansoni* (Mungomba & Kalumba 1995). No significant differences between infected and non-infected individuals were found in Brazil (Proietti & Antunes 1989). Prata (1982) concluded for a variety of abdominal symptoms that they may be, but are not necessarily associated with *S. mansoni*.

Two recent studies carried out in Ethiopia (Hailu *et al*. 1995) and Tanzania (Booth *et al*. 1998) gave promising results for the use of reported blood in stool for rapid screening of *S. mansoni*. Unfortunately, these studies followed slightly different protocols, so care is needed in the comparison of the results. In view of all these findings, there was a clear need to design a series of studies that would elucidate whether questionnaires would be useful and could be recommended for the rapid screening of *S. mansoni*.

(4)   Indirect methods

A widely used method for *S. haematobium* is the detection of blood and protein in urine using reagent stick. It is based on the fact that passing of eggs through the bladder wall causes damage, and due to these lesions small amounts of blood and proteins are also released into the urine (Wilkins *et al*. 1979, Doehring *et al*. 1985). Reagent sticks are able to detect these small amounts of blood and protein in urine, therefore they can be used as an indirect indicator for an infection with *S. haematobium*. It has been shown that the amount of blood and protein in urine correlates with the intensity of egg excretion (Wilkins *et al*. 1979), so reagent sticks provide semi-quantitative results. Over the last 20 years, numerous studies have compared reagent sticks with urine filtration and their diagnostic performance was estimated. The use of reagent sticks has been shown to be reliable, but sensitivity and specificity values varied considerably from one endemic area to another (Wilkins *et al*. 1979, Mott *et al*. 1985, Savioli *et al*. 1989, Lengeler *et al*. 1993, Mtasiwa *et al*. 1996, Mafe 1997). In view of these observations it was stressed that the diagnostic performance of reagent sticks needs to be assessed in every epidemiological setting before using this approach for large-scale community diagnosis (Feldmeier 1993).

1.5 Prevention and control of human schistosomiasis

It has been described above that the epidemiology of schistosomiasis is characterized by five important features: complexity, heterogeneity in both time and space, aggregation and sensitivity to environmental alterations. With these features in mind, it can be assumed that preventing and controlling the disease is a complicated issue and requires multifaceted approaches depending on an epidemiologically-specific mixture of interventions. Ideally, interventions should be specific to an endemic area with its observed transmission pattern, the predominant schistosome-species and intermediate snail host(s), the sanitary facilities available to the population and their water contact patterns, as well as their socio-economic status. The overall aims of prevention and control of schistosomiasis can be summarized in five points.

(1) Reduction of the number of schistosome eggs that are excreted by infected people

This is mainly achieved by chemotherapy with effective antischistosomal drugs. At present, this is the recommended strategy for schistosomiasis control, as it is directly targeted towards morbidity control (WHO 1993). This strategy only became conceivable with the advent of safe and effective drugs, and at present praziquantel is the drug of choice. It is active against all schistosome species, can be administered in a single oral dose, has high cure and egg reduction rates, and none or only mild side effects (King *et al*. 1989, Kumar & Gryseels 1994). Furthermore, it is relatively inexpensive. A series of field studies conducted in Senegal, in a community recently exposed to an intense focus of intestinal schistosomiasis (Gryseels *et al*. 1994, Stelma *et al*. 1995, Guissé *et al*. 1997) and laboratory data (Fallon & Doenhoff 1994) raised considerable concern that praziquantel-tolerance and/or resistance may be developed. There are two effective alternative drugs – oxamniquine and metrifonate – but they have become difficult to obtain in some African countries (Cioli 1998).

(2) Reduction in the number of schistosome eggs reaching freshwater environments that harbour intermediate snail host(s)

Health eduction with the ultimate aim of changing human behaviour is the key issue with regard to this objective (WHO 1990). Specific teaching materials have been developed and evaluated in the field. It is of importance that these materials are well adapted to a particualar epidemiological setting, otherwise it is likely that the message will not be understood. An example from Tanzania illustrates such a failure: children did not understand the cycle of schistosomiasis transmission, as the freshwater environment discussed was a pond, whereas the infested water source in their village was a small perennial river. Therefore, they continued to frequent the river, as they perceived no danger from this water source. It has been emphasised that teachers should play a key role in providing health education and they also showed great commitment in contributing to schistosomiasis control campaigns (Lengeler *et al*. 1991a, b, Red Urine Study Group 1995, Magnussen *et al.* 1997). The provision and use of safe and adequate sanitary facilities should also be mentioned here, as it is an important contribution towards schistosome eggs not reaching water bodies.

(3)   Reduction of contacts between miracidia and intermediate snail host(s)

This depends on all the factors mentioned above, and also to a large extent on the reduction of the density of the intermediate snail host. For about 60 years, the snail was the main target for schistosomiasis control, and reducing the snail population is still an important component of control programmes. It was clear that transmission could be halted without the snail, and it was believed that the snail was the easiest link in the cycle to break (Fenwick 1987). Several compounds toxic to the intermediate snail host have been discovered, but only niclosamide has emerged and remained commercially available on the market as a widely applied molluscicide (McCullough 1986, Fenwick 1987). In the 1950s and 60s, large-scale schistosomiasis control programmes were launched in Sudan (Sharaf el Din & El Nagar. 1955) and Egypt (Chu 1976) with the use of molluscicides. Despite impressive reductions in incidence rates, the large-scale application of molluscicides was claimed to be expensive and of limited effectiveness (re-colonization of snails immediately after application). It led to the killing of non-target organisms and was only applicable through skilled personnel (Klumpp & Chu 1987). However, extensive experiences from several African countries revealed that focal mollusciciding is effective in most habitats (Klumpp & Chu 1987). Efforts have also been put into the discovery and field-validation of molluscicides derived from plant extracts. These include *Phytolacca dodecandra* (endod) in Ethiopia (Goll *et al*. 1983), *Swartzia madagascariensis* in Tanzania (Suter *et al*. 1986), and recently also with *Jatropha curcas*, so far only in the laboratory (Liu *et al*. 1997).

In view of the limitations associated with molluscicides, ecologically less risky approaches have attempted to reduce snail densities by environmental management or by means of biological control (Madsen 1990, 1992). Although methods of biological control of intermediate snail hosts are still under development, some promising results were obtained with the introduction of competitor snails (Pointier & McCullough 1989, Pointier 1993). Predators and parasites of intermediate snail hosts may become suitable biocontrol agents; however as yet, virtually no research is focused on this topic (Madsen 1990).

(4)   Reduction of the probability of humans encountering cercariae

All three of the measures discussed above should contribute to this goal. In addition, it is of great importance for humans to decrease the frequency and duration of their contacts with infested freshwater bodies (Kloos *et al*. 1997, Useh & Ejezie 1999). This can only be achieved by changing human behaviour, for example through increasing awarness about the mode of transmission and the impact of the disease in health education campaigns (Useh & Ejezie 1999). Furthermore, the development of more satisfactory water supply schemes for domestic use should be promoted.

(5)   Damaging or killing of schistosomula

This is a novel approach which has only recently been discussed in the literature. The basis is given by the fact that after cercariae have penetrated the human skin, they become schistosomula. According to the schistosome species, it takes 4-8 weeks before they develop to adult egg-laying schistosomes (Clegg 1965, Smith *et al*. 1976). Pathological changes due to schistosomiasis are caused by the excretion of eggs. Therefore, if schistosomula are prevented from developing into egg-laying adults, the human host will be protected. The term 'chemoprophylaxis' has been used to describe this concept. The drug artemether was found in a series of laboratory experiments with rabbits and dogs infected with *S. japonicum* to kill schistosomula more effectively than adult worms (Xiao *et al*. 1995, 1998). Artemether was already in wide use against malaria and was already known to have no or only few side effects (Klayman 1985, White 1994, McIntosh & Olliaro 1999), so trials could safely be started in humans. In seven randomized control trials in China with more than 4,500 individuals exposed to *S. japonicum*, the prophylactic effect of artemether had been confirmed convincingly (Xiao *et al*. 2000a). To see whether similar effects were produced with *S. mansoni*, laboratory experiments with mice and hamsters were conducted and the prophylactic effect of artemether against this schistosome species could also be confirmed (Xiao *et al*. 2000b). In view of these findings it was recommended to conduct a randomized double-blind placebo-controlled trial to assess the prophylactic effect of oral artemether to prevent *S. mansoni* infections.

1.6   Conclusion

Concluding from these five introductory sections, methods described above are all being used in the present work. Aspects where more information needed were identified and form the objectives of this thesis. Taking advantage of the extremly focal and aggregated nature of schistosomiasis, our findings should find direct application in the field and therefore improve and refine schistosomiasis control measures.

The studies described in the present thesis include the validation of the questionnaire method for *S. haematobium* in new settings, prior to its wide-scale application in major national control programmes. This was followed by an extensive investigation of possible ways of extending the method for *S. mansoni* infection. Concurrent intestinal infections were also investigated and assessed whether questionnaire could also be used for rapid identification of amoebiasis. Finally, in one of the areas where data on *S. mansoni* had been collected for the questionnaire study, the first randomized clinical trial was carried out to assess the prophylactic effect of oral artemether against *S. mansoni* infections.

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2 Goal and Objectives

2.1 Goal

To develop and validate novel approaches contributing to a more efficacious control of human schistosomiasis. Particular consideration is given to the rapid identification of individuals and/or communities at highest risk of infection with *Schistosoma mansoni* and *S. haematobium* and on the prophylactic effect of artemether against *S. mansoni* infections.

2.2 Objectives

1   To adopt, apply and validate the "indirect questionnaire approach" for rapid assessment of high risk communities of urinary schistosomiasis in central Côte d'Ivoire.

2   To evaluate the diagnostic performance of a simple school questionnaires for the rapid identification of individuals and/or communities at highest risk of infection with urinary schistosomiasis in the Niger State, Nigeria.

3   To assess signs and symptoms of intestinal schistosomiasis that are commonly perceived by children in areas where *S. mansoni* is endemic.

4   To determine the potential of simple anamnestic questions and recalled water contact patterns for rapid identification of children with an infection with *S. mansoni*.

5   To evaluate the diagnostic performance of a simple school questionnaire for rapid and large-scale screening of intestinal schistosomiasis at the community level.

6   To assess the prophylactic effect of oral artemether against *S. mansoni* infections among schoolchildren in a highly endemic area in Côte d'Ivoire.

7   To assess adverse events and reported morbidity episodes due to oral artemether.

3   **Identification rapide par questionnaire des principaux foyers de bilharziose urinaire au centre de la Côte d'Ivoire**

E. K. N'Goran [1,2,$],   J. Utzinger [2,3],   M. Traoré [2],   C. Lengeler [3],   M. Tanner [3]

1   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

2   Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   Institut Tropical Suisse, Département d'Epidémiologie et de Santé Publique, CH–4002 Bâle, Suisse

$ Auteur de correspondance
     Tel: + 225 48 63 38
     Fax: + 225 44 03 07 / + 225 45 12 11
     e-mail: csrs@globeaccess.net

3.1   Resumé

La mise au point d'un questionnaire simple, utilisé en milieu scolaire, a présenté un intérêt pour identifier les communautés les plus touchées par la bilharziose urinaire dans plusieurs pays Africains. En Côte d'Ivoire, cette approche n'a pas été véritablement évaluée. Cette étude vise donc à en évaluer l'acceptabilité et la faisabilité. La version originale du questionnaire, proposée par l'OMS/TDR, a été modifiée pour l'adapter aux principales affections rencontrées. Au total, le questionnaire a été distribué dans 136 écoles primaires et six semaines après, 124 (91,2%) l'ont retourné avec 12 479 élèves interrogés. Les enseignants de 60 écoles formés à l'utilisation des bandelettes réactives à la microhématurie ont examiné 5 959 écoliers. Les résultats obtenus par les maîtres ont été validés dans 14 écoles par une équipe biomédicale à l'aide de la filtration des urines et des bandelettes. Les bandelettes ont présenté une bonne spécificité (97%) et une sensibilité moyenne (67%). Les réponses aux questions clés "sang dans les urines" et "bilharziose urinaire" présentent une corrélation statistique très significative avec les résultats des bandelettes (coefficients de corrélation de rangs de Spearman, $p < 0.0001$). Nos résultats sont comparés à ceux obtenus antérieurement dans les autres pays. Cette étude a en outre permis d'établir une carte géographique de la bilharziose dans la zone d'étude. Pour le programme national de lutte en phase de planification, l'approche par questionnaire est recommandée comme première étape, pour identifier les communautés les plus infectées, afin de mieux gérer les ressources qui restent bien souvent limitées.

Mots clés: bilharziose urinaire – Côte d'Ivoire – identification rapide – programme national de lutte

Abstract

The development of a simple questionnaire for use with schoolchildren proved to be a feasible way to identify the communities that are at highest risk for urinary schistosomiasis in several African countries. The chief purpose of the present study was to assess the acceptance and feasibility of this approach in the Côte d'Ivoire, where it had not yet been evaluated. Questionnaires were distributed to 136 primary schools in central Côte d'Ivoire and were returned within 6 weeks by 124 schools (91.2%) with a total of 12,479 schoolchildren interviewed. Teachers of 60 schools were trained to apply reagent stick testing to identify microhaematuria, and within two weeks they screened a total of 5,959 children. In 14 selected schools a validation of the teacher's results was carried out by a biomedical team, applying reagent stick testing and urine filtration. Reagent sticks showed a high specificity (97%) and a moderate sensitivity (67%). The two key questions about "blood in urine" and "having had schistosomiasis" showed highly statistically significant correlations with reagent stick testing results (Spearman rank correlation, $p < 0.0001$). Our results are in good agreement with previous findings from elsewhere. This study also allowed to draw a map with the actual

distribution of urinary schistosomiasis in the study area. For the national control programme which is currently in a planning phase, it is recommended that the questionnaire approach should be applied as a first step to identify the communities at highest risk of urinary schistosomiasis, so that limited resources can be better concentrated on those communities.

Key Words: Urinary schistosomiasis – Questionnaire survey – National control programme – West Africa

3.2 Introduction

Les maladies transmissibles demeurent les problèmes majeurs de santé dans les pays en développement. Cette réalité peut être illustrée par l'exemple de la bilharziose, qui est endémique dans 74 pays dans le monde, atteignant au moins 200 millions de personnes et auxquelles 600 millions sont exposées au risque d'infection (1). En Afrique, la bilharziose urinaire est couramment rapportée dans 44 pays, mais malgré cette importance, les programmes de lutte à l'échelon national constituent plutôt l'exception que la règle (1).

Du fait de la répartition très focale de la bilharziose (2, 3), il est essentiel de consacrer les moyens souvent limités aux régions les plus infectées. D'où tout l'intérêt d'une approche capable de déterminer rapidement, à un faible coût mais avec une bonne fiabilité, si une communauté présente ou non un risque élevé d'infection (4, 5). Lengeler et coll. (6) ont mis au point en Tanzanie un questionnaire très simple destiné aux élèves, qui s'est révélé performant pour l'identification rapide des communautés à haut risque d'infection à l'échelle d'un district. En l'espace de six semaines, à un coût bien moindre que les examens parasitologiques, les communautés à niveau élevé d'infection de bilharziose urinaire ont pu être identifiées. Cette approche a par la suite été validée dans un district voisin (7), puis dans sept autres pays Africains (8). Mis à part l'unique exception que constitue l'Ethiopie (9), il a été observé une bonne corrélation entre les résultats du questionnaire et ceux des examens biomédicaux; les écoles présentant un faible niveau d'infection de bilharziose urinaire pouvaient ainsi être exclues avec une bonne sécurité. Cela a conduit à suggérer que la nécessité d'autres validations ne soit limitée qu'aux cas où le questionnaire initial faisait l'objet de profondes modifications, dans des contextes épidémiologiques nouveaux et dans les endroits où les autorités sanitaires émettaient des réserves sur la méthode (10).

En Côte d'Ivoire, seules quelques études ponctuelles ont été conduites chez l'homme pour évaluer l'importance de la bilharziose (11-16) et les données à l'échelle du district manquent. Il est donc impossible de faire un estimation de l'importance de l'endémie au niveau national et par conséquent d'envisager une comparaison de la situation prévalant en Côte d'Ivoire à celle des pays où le questionnaire a été validé avec succès. Considérant les biais liés aux enquêtes par questionnaire, les autorités sanitaires ont initialement manifesté des réserves sur l'efficience d'une telle approche basée simplement sur les réponses des élèves. Mais suite aux données

obtenues dans les autres pays Africains ils ont montré un grand intérêt pour les résultats de la validation en Côte d'Ivoire. De plus, deux enquêtes préliminaires ont montrées que des approches indirectes pourraient aider à identifier les communautés prioritaires pour le contrôle de la bilharziose urinaire (17, 18).

Prenant en compte ces observations, mais aussi le fait que le programme national de lutte est en cours d'élaboration, nous avons jugé opportun de valider en Côte d'Ivoire l'approche par questionnaire pour identifier les communautés à haut risque de bilharziose urinaire. L'objectif étant de contribuer à la validation et d'évaluer l'acceptabilité et la faisabilité de l'approche par questionnaire, puis de comparer les résultats à ceux obtenus ailleurs. Avec des travaux complémentaires sur la bilharziose intestinale, qui sont en cours depuis le début de 1997 (19), l'ensemble de ces recherches pourrait fournir la base pour mieux planifier et mettre en œuvre un programme national de lutte contre les schistosomoses.

3.3   Matériels et Méthodes

Zone d'étude

Cette étude a été conduite dans 5 sous-préfectures: Toumodi, Djékanou, Kokumbo, Tiassalé et Taabo, situées au sud de la partie centrale de la Côte d'Ivoire. Cette zone couvre une superficie totale de 6 181 km^2. Le climat est du type subéquatorial (20) et la végétation dominante est la savane. La moyenne annuelle des précipitations est de 1 060 mm. La saison des pluies dure 8 mois et s'étend du mois d'avril au mois d'octobre, avec une forte baisse des précipitations durant les mois de juillet et août (21). Dans les villages, les populations à majorité agriculteurs, cultivent surtout l'igname et le manioc. Trois villes, avec des densités de populations humaines plus importantes que les villages ont aussi été concernées par cette étude: Toumodi, Tiassalé et N'Douci. Les écoles primaires de la zone sont organisées en trois inspections de l'enseignement (Toumodi, Tiassalé 1 et Tiassalé 2; Figure 3.1). Ces inspections regroupent au total 156 écoles et comptaient 34 509 élèves au cours de l'année scolaire 1996/97. Le paludisme est holoendémique dans la région et l'onchocercose est fréquemment signalée. En ce qui concerne la bilharziose, les informations disponibles restent éparses à l'exception des données publiées récemment (16) qui ont montré que la bilharziose urinaire sévissait à l'état d'hyperendémie dans des villages autour de la retenue d'eau du barrage de Taabo.

Questionnaire destiné aux élèves

La version française originale du questionnaire destiné aux élèves, proposée par Chitsulo et coll. (10), a été pré-testée après discussion avec les responsables sanitaires de la sous-préfecture de Toumodi. Ce pré-test a concerné toutes les classes de deux écoles. Il en est résulté des modifications importantes, concernant à la fois les symptômes et les maladies pour tenir compte de la situation épidémiologique de la région. Finalement, sept symptômes de la liste initiale ont été retenus, trois changés ("corps qui chauffe", "corps qui gratte" et "ventre qui coule" au lieu de "fièvre", "démangeaisons" et "diarrhée") et un symptôme a été rajouté ("vomi"). La liste des maladies a été portée de neuf à douze en ne retenant que cinq de la liste initiale. Les sept maladies nouvelles sont les suivantes: "diarrhée", "asthme", "plaies", "pian", "rhume", "gale" et "bilharziose intestinale". Le pré-test ayant montré que les élèves des petites classes, en particulier ceux du CP1 et CP2, avaient beaucoup de difficultés à répondre aux questions; l'interview dans ces classes pouvait durer toute la journée au lieu de 1 à 2 heures dans les plus grandes classes. Nous avons donc choisi de ne soumettre le questionnaire qu'aux plus grandes classes: CE2, CM1 et CM2. Une copie de la version finale du questionnaire est proposée en annexe.

Le questionnaire a été expédié dans toutes les écoles ayant les classes de CE2, CM1 et CM2, soit au total 136 écoles (Toumodi: 57, Tiassalé 1: 45 et Tiassalé 2: 34). Il a été demandé aux maîtres de ces classes d'interroger individuellement leurs élèves, en utilisant une classe vide à l'intérieur de laquelle ils les invitaient un à un pour l'interrogatoire, afin de s'assurer que les élèves interrogés ne communiquent pas avec ceux qui attendaient de l'être.

Validation du questionnaire: Recherche de la microhématurie par les maîtres

A Toumodi, 52 écoles (91,2%) avaient retournées le questionnaire et 19 écoles, choisies au hasard, ont été retenues pour les tests biomédicaux. Le directeur et un maître de chaque école retenue ont été invités à une formation d'une journée à l'inspection de l'enseignement de Toumodi. Après une brève présentation de la bilharziose, on apprenait aux enseignants comment utiliser les bandelettes réactives (Sangur-Test, Boehringer Mannheim, Allemagne) pour rechercher, à partir des instructions du fabriquant, la microhématurie. Les résultats des bandelettes étaient regroupées en 3 catégories: négatif, 1+ et 2+ (2+ regroupait le 2+ et le 3+ de la liste du fabriquant). Il était précisé aux maîtres que la collecte des urines ne devait se faire qu'entre 10 et 14 heures. Séance tenante, les enseignants ont participé à une démonstration portant sur une cinquantaine d'enfants d'une école voisine. Au terme de la formation, chaque enseignant est reparti avec un équipement composé de pots de collecte des urines, de bandelettes réactives, de gants, de produits sanitaires (seau, savon, eau de Javel) et de fiches d'enregistrement des résultats. Il leur a été demandé de procéder à l'examen des élèves les jours suivants et de faire parvenir les résultats à leur inspection de l'enseignement.

A Tiassalé 1 et 2, 72 écoles (91,1%) ont retourné les questionnaires. Suivant les réponses des enfants et en tenant compte des résultats préliminaires obtenus à Toumodi, les écoles ont été classées en deux groupes. Les écoles avec un seuil de positivité dépassant 30% pour la question "j'ai eu du sang dans les urines" et les écoles avec un seuil de positivité plus faible à la même question. Toutes les 15 écoles avec un seuil de positivité dépassant 30% furent retenues pour la validation. Parmi les 57 écoles restantes, 26 ont été choisies au hasard et ont également été retenues. Tout comme à Toumodi, une journée de formation regroupant les directeurs et un maître de chaque école a été organisée. Là aussi, après la phase pratique, chaque enseignant est reparti avec les mêmes équipements et les mêmes instructions. Au total donc, un examen avec les bandelettes a été effectué par les maîtres dans 60 écoles.

Vérification du travail des maîtres

A Toumodi, 14 écoles choisies au hasard parmi les 19 concernées par la recherche de la microhématurie par les maîtres ont été retenues pour évaluer les résultats des maîtres, par des tests croisés réalisés par une équipe biomédicale. Cette équipe biomédicale composée de deux chercheurs expérimentés, a visité l'ensemble de ces 14 écoles, en examinant les mêmes enfants que les maîtres. Les échantillons d'urines prélevés entre 10 et 14 heures ont été testés avec les bandelettes réactives en retenant les mêmes catégories que les maîtres. De plus, une filtration de 10 ml d'urines a été réalisée sur du tissu Nytrel suivant la méthode de Plouvier et coll. (22). Les résultats de la filtration des urines ont été considérés comme référence et ont permis de comparer les résultats obtenus par bandelettes réactives. La comparaison des résultats obtenus par l'équipe biomédicale et ceux obtenus par les maîtres a permis de vérifier la qualité du travail des maîtres.

Localisation des écoles et soins par chimiothérapie des élèves

Une équipe composée d'un infirmier des grandes endémies de Tiassalé et de deux chercheurs est retournée dans toutes les 60 écoles concernées par l'évaluation biomédicale. A cette occasion, la position exacte de chaque école a été relevée à l'aide d'un GPS 45 (Garmin Corp., Lenexa, USA) pour la réalisation de la carte de répartition des foyers de bilharziose urinaire. Tous les enfants trouvés positifs par la recherche de la microhématurie et tous ceux excrétant des œufs de *Schistosoma haematobium* dans les urines ont alors reçu une dose orale unique de praziquantel suivant la posologie standard recommandée par l'OMS de 40 mg/kg de poids corporel (1).

Traitement et analyse des données

Une base de données informatique a été constituée à l'aide du logiciel EpiInfo (version 6.04) à partir de l'ensemble des données recueillies avec le questionnaire et lors des enquêtes biomédicales. Une large et complète vérification a été effectuée pour assurer la cohérence des données. Les fréquences des réponses aux deux questions clés "sang dans les urines" et "bilharziose urinaire" ont pour toutes les écoles été comparées aux fréquences calculées

manuellement à partir des fiches initiales. Les résultats des tests biomédicaux ont quant à eux fait l'objet d'une double entrée et une validation directement à partir du logiciel. Toutes les anomalies ont alors été corrigées en se référant aux fiches originales des données.

La sensibilité, la spécificité et les valeurs prédictives ont été calculées entre les deux méthodes: filtration des urines et bandelettes réactives. Pour calculer ces paramètres, les résultats biomédicaux ont été regroupés en deux catégories: négatifs (absence d'œufs de *S. haematobium* dans les urines; bandelette négative) et positifs (œufs de *S. haematobium* dans les urines; bandelette positive). Les résultats obtenus par les bandelettes réactives ont été comparés entre l'équipe biomédicale et les maîtres en calculant le coefficient de convergence Kappa, pour chacune des trois catégories retenues lors de la lecture. Une analyse de la régression linéaire a été réalisée entre les pourcentages de réponses positives aux questions ("sang dans les urine" et "bilharziose urinaire") et les prévalences de microhématuries ($\geq 1+$) observées par les maîtres, à l'aide du coefficient de corrélation de rangs de Spearman. Finalement, nos résultats ont été comparés à ceux obtenus antérieurement dans les autres pays Africains par analyse de la régression linéaire et du coefficient de corrélation de rangs de Spearman.

3.4   Résultats

Résultats opérationnels (Figure 3.1)

Les questionnaires ont été expédiés à 136 écoles primaires des inspections de Toumodi, Tiassalé 1 et Tiassalé 2 (effectif d'inscrits dans les classes CE2, CM1 et CM2: 14 821). Six semaines après, 124 écoles (91,2%) les avaient correctement remplis et renvoyés. Au total, 12 479 élèves (90,6%) sur les 13 463 inscrits dans ces classes ont été interrogés par leurs maîtres. Leur âge était de 7 à 16 ans avec une moyenne de 12,0 ± 1,6 ans. Le sex-ratio entre garçons et filles a été de 1,5:1, et le nombre moyen d'enfants interrogés par école de 100,6 ± 33,1 (minimum 30 et maximum 220).

Deux séminaires d'une journée chacun ont été organisés à l'intention des enseignants des 60 écoles sélectionnées pour la validation, afin de leur apprendre à utiliser les bandelettes réactives. Deux semaines après chacune de ces formations, les enseignants avaient examiné tous les enfants des classes CE2, CM1 et CM2 (effectif d'inscrits: 6 371), et retourné les fiches avec les résultats, correctement remplies, à l'inspection de l'enseignement. Le nombre total des élèves ainsi examinés fût de 5 959 (93,5%); la moyenne d'âge de 12,0 ± 1,6 ans; le sex-ratio entre garçons et filles de 1,6:1 et le nombre moyen d'élèves examinés par école de 99,3 ± 31,5 (minimum 31 et maximum 191). Ces valeurs étaient comparables à celles obtenues avec les enfants interrogés et nous avons considéré que l'échantillon choisi était représentatif de la population scolaire concernée. Les résultats obtenus avec les bandelettes réactives ont été les suivants: 1 464 élèves positifs (24,6%) si le seuil de positivité est considéré à la limite 1+ et

852 élèves (14,3%) lorsqu'il est porté à 2+. Les pourcentages respectifs des réponses affirmatives aux deux questions clés "j'ai eu la bilharziose urinaire" et "j'ai eu du sang dans les urines" sont de 16.8% et 20.9%, pour l'ensemble des 60 écoles.

Etape 1 - Questionnaire et classification	Toumodi	Tiassalé 1	Tiassalé 2
• Questionnaire envoyé à toutes les écoles (n=136) par l'inspection de l'enseignement (effectif d'inscrits: 33167)	57	45	34
• Elèves des classes CE2, CM1 et CM2 intérrogés individuellement (effectif d'inscrits: 14821)			
• Réponses des 124 écoles (91,2%) après 6 semaines (effectif d'inscrits: 13463 ; total réponses: 12 479)	52 (91,2%)	38 (84,4%)	34 (100%)
• Classification: Seuil: 30% des élèves ayant répondu "oui, j'ai eu du sang dans les urines"	non	oui ≥ 30%: 15 < 30%: 57 15 26	
• 60 écoles choisies (effectif d'inscrits: 6371)	19		
Etape 2 - Validation par les maîtres			
• Séminaire pour former les maîtres à la détection de microhaematurie par bandelettes	1 jour	1 jour	
• Résultats de maîtres (après 2 semaines) Total: 5959 élèves examinés (93.5%)	19 (100%)	41 (100%)	
Etape 3 - Vérification du travail des maîtres			
• Equipe biomédicale (filtration, bandelettes)	14	41	
Etape 4 - Traitement des enfants			
• Dose unique de praziquantel (40 mg/kg) Total: 1464 élèves	Tous les enfants: microhématurie≥ 1+		
Etape 5 - Elaboration d'une carte de répartition			
• Coordonnées géographiques des écoles et géoréférence sur une image satellite	Répartition des foyers à risque		
• Classification par seuil d'infection			

Figure 3.1

Enquête par questionnaire sur la bilharziose urinaire en Côte d'Ivoire: protocole expérimental et résultats opérationnels de l'étude.

Vérification des résultats biomédicaux

L'équipe biomédicale a procédé à une vérification croisée des résultats sur 1 336 élèves (soient 22,4% des élèves testés par les maîtres) provenant de 14 écoles. Pour cette enquête la moyenne d'âge était 12,2 ± 1,6 ans, le sex-ratio entre garçons et filles était 1,7:1 et le nombre moyen d'élèves examinés par école de 95,4 ± 26,3 (minimum 50 et maximum 132). Ces valeurs sont comparables à celles de toutes les 60 écoles.

La comparaison des résultats de la filtration des urines avec les bandelettes (Tableau 3.1) a montré une très bonne spécificité de 96,5% (95% intervalle de confiance (IC): 95,3%-97,5%) et une sensibilité moyenne de 66,7% (95% IC: 58,5-73,9%). La valeur prédictive négative était 95,7% (95% IC: 94,4-96,8%) et la valeur prédictive positive 71,3% (63,1-78,4%). La régression linéaire entre la prévalence parasitologique (œufs dans les urines) et la microhématurie de toutes les 14 écoles a eu pour résultat une très bonne corrélation (r = 0,98; p < 0,0001). La corrélation pour la microhématurie ≥ 1 était encore plus bonne que pour la microhématurie ≥ 2. Cette analyse a ensuite permis d'établir la correspondance entre la prévalence mesurée par la filtration d'urine et la prévalence mesurée par les bandelettes:

Prévalence parasitologique = 1,20 * prévalence de microhématurie (³ 1+) – 0,88

Tenant compte de ce résultat, les prévalences parasitologiques de 25% et 50%, souvent considérées comme seuils d'infection moyen et élevé (1), correspondent à des prévalences de microhématuries de 21,5% et 42,3%.

Tableau 3.1
Enquête sur la bilharziose urinaire: comparaison entre les résultats obtenus par filtration des urines et par bandelettes réactives par une équipe biomédicale.

		Filtration des urines		Total
		+	–	
Bandelettes réactives	+	102	41	**143**
	–	51	1 142	**1 193**
	Total	**153**	**1 183**	**1 336**

La comparaison des résultats des bandelettes réactives de l'équipe biomédicale et des maîtres est présentée au Tableau 3.2. En prenant en compte toutes les 3 catégories (0, 1+ et 2+), on observe une convergence hautement significative avec un coefficient Kappa de 0,52 (p < 0,0001). En regroupant tous les résultats positifs (1+ et 2+) dans une seule catégorie, le coefficient Kappa augmente à une valeur de 0,66 (p < 0,0001). Ces résultats suggèrent clairement que les maîtres ont fait un travail de qualité, et cela nous a permis d'utiliser leurs résultats pour la validation des questionnaires.

Tableau 3.2

Enquête sur la bilharziose urinaire: comparaison des résultats des bandelettes réactives obtenues par une équipe biomédicale et par des maîtres d'école.

		Equipe biomédicale			
		2+	1+	négatives	**Total**
Maîtres	2+	35	20	13	**68**
	1+	18	25	32	**75**
	négatives	12	28	1 153	**1 193**
	Total	**65**	**73**	**1 198**	**1 336**

Réponses des élèves et validation avec les bandelettes réactives par les maîtres

Les prévalences d'hématuries obtenues par les maîtres (≥ 1+) et les réponses positives des élèves aux deux questions clés ("bilharziose urinaire" et "sang dans les urines") dans les trois inspections de l'enseignement sont données dans le Tableau 3.3. Les coefficients de corrélation de rang de Spearman entre les résultats obtenus par les maîtres et les réponses aux deux questions clés sont pour toutes les trois inspections statistiquement significatifs. En regroupant les résultats des trois inspections (n = 60 écoles), les coefficients de rang de Spearman obtenus révèlent une corrélation très hautement significative entre les réponses aux deux questions "bilharziose urinaire" (p < 0,0001) et "sang dans les urines" (p < 0,0001).

Tableau 3.3

Prévalences de microhématuries (≥ 1+) relevées par les maîtres et pourcentage de réponses positives aux deux questions clés "j'ai eu la bilharziose urinaire" et "j'ai eu du sang dans les urines" dans les trois inspections de l'enseignement. Rho indique le coefficient de corrélation de rangs de Spearman entre les tests biomédicaux et les réponses des élèves (*: p < 0.05, **: p < 0.001).

Inspection	Ecoles n	Microhématurie (≥ 1+)		"Bilharziose urinaire"			"Sang dans les urines"		
		pos/tot	%	pos/tot	%	Rho	pos/tot	%	Rho
Toumodi	19	191/1958	9,8	175/1932	9,1	0,61 *	231/1932	12,0	0,53 *
Tiassalé 1	19	753/1973	38,2	457/1937	23,6	0,80 **	552/1937	28,5	0,85 **
Tiassalé 2	22	520/2028	25,6	360/2035	17,7	0,80 **	448/2035	22,0	0,80 **
Total	60	1464/5959	24,6	992/5904	16,8	0,78 **	1231/5904	20,9	0,83 **

La comparaison entre la microhématurie (≥ 1+) et les réponses positives des élèves aux questions "bilharziose urinaire" et "sang dans les urines" de l'ensemble des écoles est présentée à la Figure 3.2. Le coefficient de la régression entre la question "sang dans les urines" et les résultats des bandelettes réactives a une valeur de r = 0,90 (95% IC: 0,84-0,94), un peu plus élevée que celle de la question "bilharziose urinaire" (r = 0,85; 95% IC: 0,75-0,91).
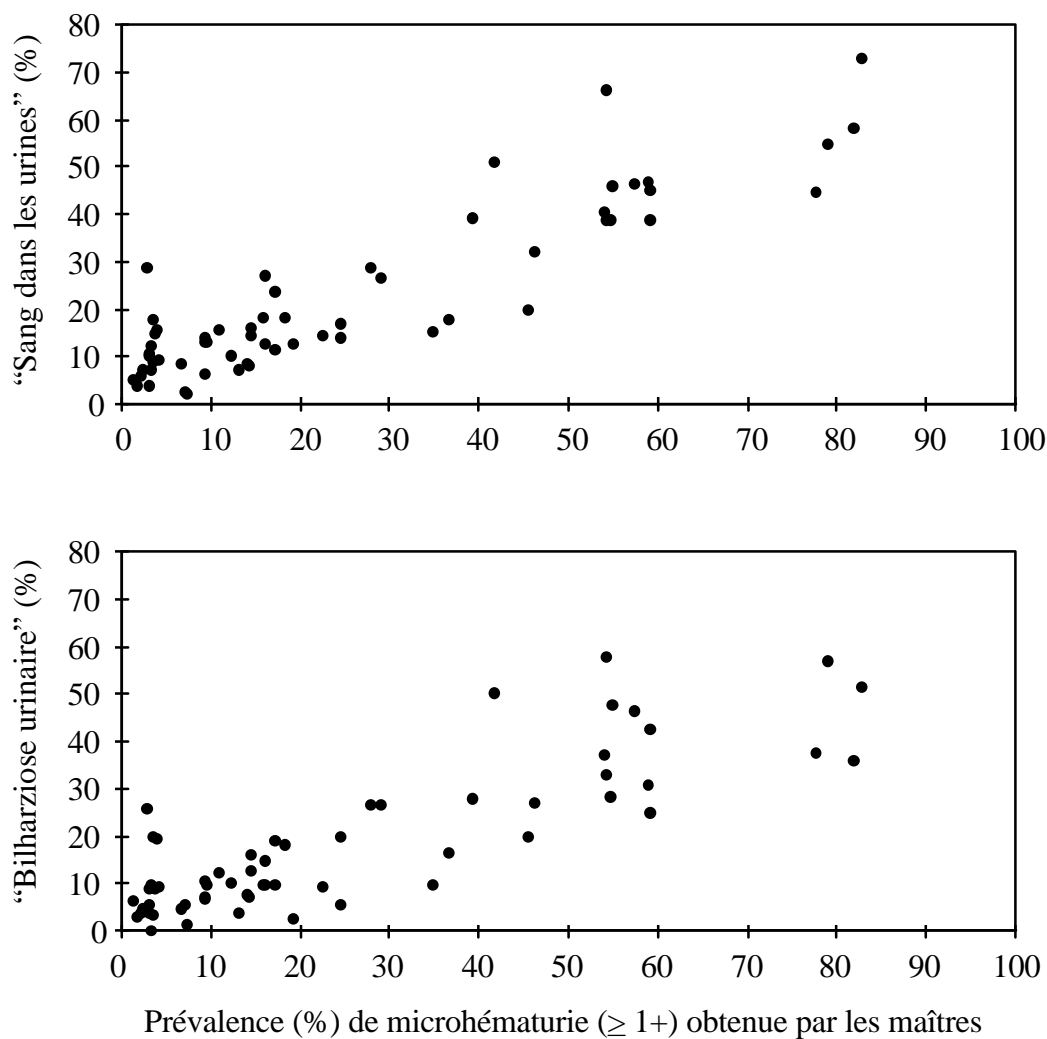
Figure 3.2

Enquête par questionnaire sur la bilharziose urinaire en Côte d'Ivoire: corrélation entre la prévalence des réponses positives des élèves aux deux questions clés et les prévalences obtenues avec les bandelettes réactives dans l'ensemble des 60 écoles ayant fait l'objet de la validation par les tests biomédicaux.

Performance diagnostique du questionnaire

La sensibilité, la spécificité et les valeurs prédictives positives et négatives des deux questions "bilharziose urinaire" et "sang dans les urines" pour les deux différents seuils de prévalence d'hématurie (moyen: 21,5%; élevé: 42,3%) sont présentés au Tableau 3.4. Les deux questions donnent une sensibilité élevée et une bonne spécificité pour détecter les écoles à moyen ou haut taux d'infection. Les valeurs prédictives négatives présentent un intérêt particulier, dans la mesure où elles indiquent avec quelle probabilité une école présentant un faible risque d'infection serait correctement exclue en se basant uniquement sur les résultats du questionnaire. Quand le seuil de microhématurie est porté à 42,3%, les valeurs prédictives négatives obtenues sont supérieures à 93% pour les deux questions.

Tableau 3.4

Enquête sur la bilharziose urinaire en Côte d'Ivoire: performance diagnostique du questionnaire pour l'identification des écoles à risque moyen ou élevé de schistosomose urinaire (n = 60 écoles).

| | Seuil de prévalence de microhématuries ≥ 1+ | | | |
| | "Bilharziose urinaire" | | "Sang dans les urines" | |
	Moyen (21,5%)	Elevé (42,3%)	Moyen (21,5%)	Elevé (42,3%)
Seuil de positivité du questionnaire	16,2%	27,5%	19,8%	33,3%
Sensibilité (95% IC)	88% (67-97%)	80% (51-95%)	79% (57-92%)	87% (58-98%)
Spécificité (95% IC)	86% (70-95%)	96% (84-99%)	92% (76-98%)	96% (84-99%)
Valeur prédictive positive (95% IC)	81% (60-93%)	86% (56-98%)	86% (64-96%)	87% (58-98%)
Valeur prédictive négative (95% IC)	91% (75-98%)	94% (81-98%)	87% (71-95%)	96% (84-99%)

Répartition de la bilharziose urinaire

Toutes les écoles situées autour du lac artificiel de Taabo ou le long du fleuve Bandama en amont du lac sont caractérisées par de fortes prévalences. A l'opposé, les écoles situées en aval du barrage, le long du fleuve sont moins infectées. Deux autres zones présentent des niveaux d'infection élevés: Morokro (dans la partie centrale) puis Batéra, Binao et Bodo dans le sud-ouest de la zone d'étude. Toutes les écoles des zones urbaines ont des taux d'infection inférieurs à 21,3%.

Comparaison avec les résultats des autres pays

Jusqu'à présent la relation entre la microhématurie mesurée avec des bandelettes réactives, et les réponses aux questions "bilharziose urinaire" et "sang dans les urines" a été constante en Afrique (8). L'analyse par régressions linéaires des données obtenues antérieurement en Tanzanie (7) puis dans sept autres pays Africains (8), et les résultats présentés ici, montre une corrélation statistique hautement significative entre les réponses aux deux questions clés "sang dans les urines" (r = 0,97, p < 0,0001) et "bilharziose urinaire" (r = 0,91, p = 0,0007) et la prévalence globale de microhématurie (Figure 3.3). En Côte d'Ivoire, la prévalence globale d'hématurie classerait le pays au dessus du Congo, du Zaïre et de l'Ethiopie et en dessous de la Zambie, du Zimbabwe, du Malawi, de la Tanzanie et du Cameroun. Les deux questions clés "bilharziose urinaire" et "sang dans les urine" donnent des taux de positivité situés au dessus de la droite de régression établie sur la base des résultats obtenus dans ces neuf pays.
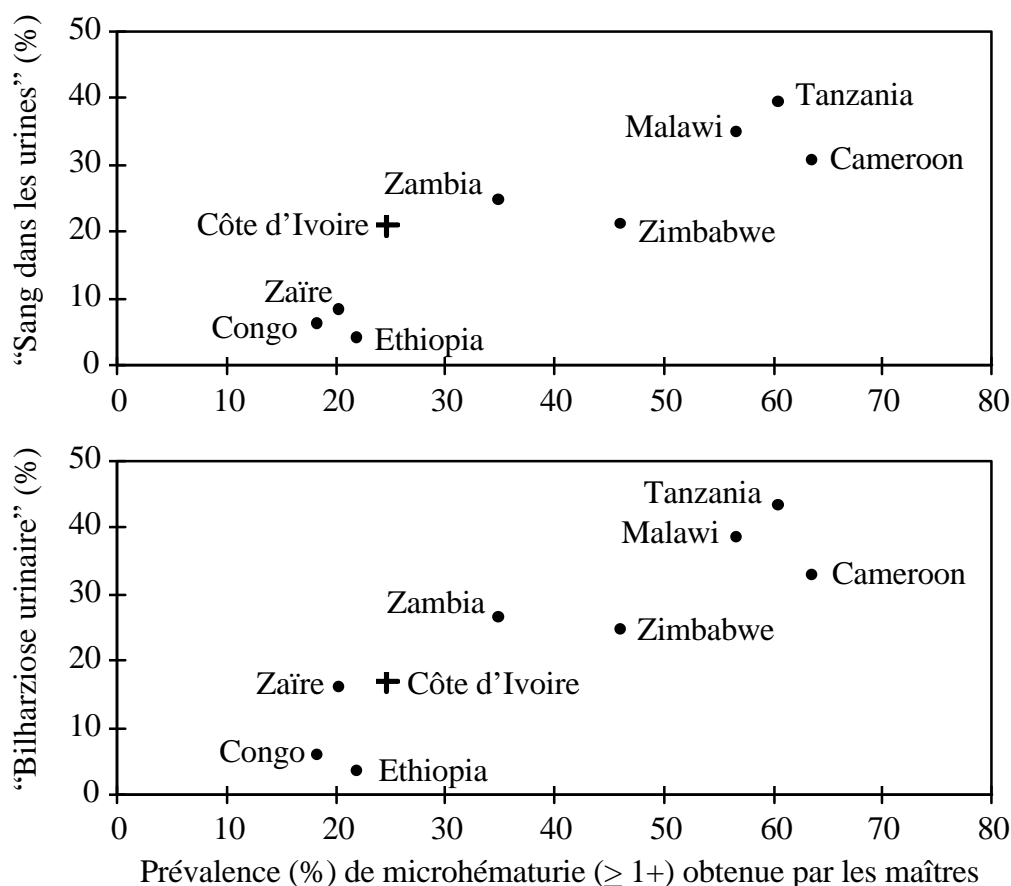
Figure 3.3

Enquête par questionnaire sur la bilharziose urinaire en Côte d'Ivoire: analyse des régressions linéaires obtenues dans différents pays aricains, entre la prévalence globale de microhématurie et les réponses des élèves aux deux questions clés (•: données fournies par Lengeler et coll. (7) et par le Red Urine Study Group (8), +: nos données).

3.5   Discussion

Vers la fin des années 1980, Lengeler et coll. (6) ont mis au point une méthode d'approche simple, par questionnaire utilisé en milieu scolaire, pour identifier les communautés à haut risque de transmission de la bilharziose urinaire, au niveau d'un district, en zone rurale Tanzanienne. Cette méthode a d'abord été validée dans un district voisin (7), puis dans sept autres pays africains (8). De bonnes corrélations ont été trouvées entre les réponses des élèves aux deux questions clés "j'ai eu la bilharziose" et "j'ai eu du sang dans les urines" et la microhématurie testée par une équipe biomédicale ou par les maîtres. Ces études ont aussi montré que l'approche par le questionnaire était rapide, d'un très bon rapport coût-efficacité (6-8, 23-26), et qu'elle avait de plus des chances d'être utilisée avec succès dans d'autres environnements. Des travaux récents confirment ces résultats (27-29).

Chitsulo et coll. (10) suggérèrent à l'issue de ces travaux que les validations ultérieures n'étaient nécessaires que dans trois situations: lorsque le contexte épidémiologique était différent; lorsque le questionnaire initial faisait l'objet de profondes modifications, et quand les autorités sanitaires émettraient des réserves sur les performances de la méthode. Dans le cas de la Côte d'Ivoire, ces trois conditions étaient remplies. L'approche par le questionnaire étant perçue comme un outil important du programme national de lutte, nous avons pensé qu'une validation permettrait de conforter les recommandations dans le cadre de ce programme.

Notre vérification croisée a aussi permis de montrer que les bandelettes réactives sont fiables pour détecter la maladie au niveau individuel. La comparaison des résultats des bandelettes à ceux de la filtration des urines donne une sensitivité moyenne et une forte spécificité, ce qui est en accord avec des résultats obtenues antérieurement dans d'autres pays Africains (30, 31). Nos résultats de spécificité et de valeurs prédictives sont encore meilleurs que ceux obtenus précédemment dans un pays voisin (32) et une région voisine (33). Par contre la sensibilité dans notre enquête était plus faible que dans ces deux études.

La validation des réponses au questionnaire a été faite à partir de la microhématurie recherchée directement par les maîtres d'école, qui avaient reçu une journée de formation. Cette approche était envisageable, dans la mesure où les résultats obtenus ailleurs ont montré un bon accord entre les équipes biomédicales et les maîtres (6, 8). Nos résultats sont conformes à cette observation. En parfait accord avec Lwambo et coll. (27), la corrélation entre une infection et la microhématurie $\geq$ 1+ était légèrement supérieure à celle de la microhématurie $\geq$ 2+. En conséquence, la recherche de la microhématurie par les maîtres a été considérée comme une méthode fiable et la comparaison des résultats obtenus avec les réponses aux deux questions clés du questionnaire pouvait être envisagée. Lors de discussions informelles, les maîtres ont insisté sur le fait qu'ils avaient été fiers de recevoir la formation à l'utilisation des bandelettes réactives, cela d'autant plus que sur la base des résultats de leurs analyses, les élèves avaient reçu le traitement médical. Ils avaient donc été heureux d'avoir ainsi contribué à l'amélioration de l'état sanitaire de leurs élèves. Des expériences très similaires ont été faites ailleurs (34), ce qui permet de recommander la participation active des maîtres, même pendant la mise en

œuvre des moyens de lutte.

D'une manière générale la question "sang dans les urines" a permis d'avoir une corrélation légèrement meilleure que celle de la "bilharziose urinaire". Cela pourrait s'expliquer en grande partie par le fait que les élèves de certaines écoles, ignorant la bilharziose urinaire comme terme, répondaient à cette question par "je ne sais pas". Cette réponse considérée comme négative lors de l'analyse, pourrait être à l'origine de la baisse du taux de réponses positives. Toutefois, même en prenant en compte cette limitation, on obtient pour les prévalences des deux questions clés des corrélations statistiques hautement significatives avec les prévalences de microhématurie. Ces résultats sont conformes à ceux précédemment trouvés en Tanzanie (6, 7, 29) et dans d'autres pays Africains (8). Lorsqu'on regroupe les données recueillies dans l'ensemble des pays, on trouve que les prévalences des deux questions donnent de très bonnes corrélations avec les taux de microhématurie relevés par les maîtres.

Cette étude aura permis une identification rapide des foyers d'infection de bilharziose urinaire et la représentation de leur répartition spatiale dans 5 sous-préfectures situées au sud de la partie centrale de la Côte d'Ivoire. Ces résultats montrent clairement que les localités situées près du lac artificiel de Taabo sont les plus exposées aux schistosomoses. Ils confirment ainsi les récentes données de l'étude de l'impact sur la santé du barrage de Taabo, utilisant comme indicateur de risque la bilharziose (16). Cela est conforme à ce qui est généralement observé ailleurs au niveau des grands barrages (35). D'autre part, la présence de cours d'eaux naturels et l'aménagement de petites retenues d'eau à vocation agricole pourraient expliquer la localisation des deux autres foyers trouvés, ce qui serait en bon accord avec Brinkmann et coll. (36).

Notre étude a clairement démontré que l'approche questionnaire est faisable, bien acceptée et donc réalisable en Côte d'Ivoire. Les résultats ayant été conformes à ceux obtenus ailleurs, cette méthode doit être considérée comme un puissant outil d'identification des foyers à haut niveau d'infection de bilharziose urinaire. Par conséquent, le questionnaire peut être recommandé comme un outil bon marché et rapide, pour le programme national de lutte. Il permettrait ainsi de cibler en priorité sur ces zones identifiées les interventions de lutte.

3.6   Remerciements

3.7   Références

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4   **Control of urinary schistosomiasis: an investigation into the effective use of questionnaires to identify high risk communities and individuals in Niger State, Nigeria**

M. A. Mafe [1,2,$],   T. von Stamm [1,3,$],   J. Utzinger [4,5],   E. K. N'Goran [5,6]

1   Schistosomiasis Workgroup Borgu (SCHWOB), Box 305, New Bussa, Niger State, Nigeria

2   Public Health Division, Nigerian Institute of Medical Research, PMB 2013, Yaba, Lagos, Nigeria

3   LAFIA PHC Project (GTZ), Box 305, New Bussa, Niger State, Nigeria

4   Department of Public Health and Epidemiology, Swiss Tropical Institute, PO Box, CH-4002 Basle, Switzerland

5   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

6   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

$ Corresponding authors
     Tel: + 234-1-774-4723
     Fax: + 234-1-5804190
     e-mail: gtzlagos@infoweb.abs.net

4.1   Summary

Schistosomiasis is a public health problem in Nigeria. Although there is a national programme for its control, there is the need for reliable and simple means of rapidly diagnosing communities to provide a detailed map on the distribution of the disease in the country, in order to prioritize control activities, as well as to monitor the effectiveness of control operations. A rapid assessment technique using school-questionnaires was tested in Borgu Local Government Area (LGA), Niger State, north-western Nigeria. Following a series of focus group discussions, the questionnaires were adapted before they were administered through the existing school system to 60 primary schools in Borgu LGA. Correctly completed questionnaires were returned from 58 schools (97%) within 4 weeks. Questionnaires were validated by reagent stick tests performed by previously trained teachers. Their results proved to be reliable when compared to those obtained by our research team in 20 randomly selected schools. Overall prevalences of microhaematuria at 1+ and 2+ levels were 45.7% and 27.1%, respectively. Highly significant correlations were obtained between school prevalence of microhaematuria and reported schistosomiasis, as well as reported blood in urine. The diagnostic performance of the questionnaires at the 2+ level of microhaematuria was very good. The design of our study also allowed data analysis on an individual level, and multivariate analysis revealed highly significant odds ratios for reported schistosomiasis and reported blood in urine to detect an individual with urinary schistosomiasis. Our results are in good agreement with previous reports from other African countries, and questionnaires can be recommended for rapid identification of communities at highest risk of urinary schistosomiasis in Nigeria, so that scarce resources of the national control programme can be used most effectively.

Key words: Nigeria – Questionnaires – Rapid assessment technique – *Schistosoma haematobium* – Urinary schistosomiasis

4.2   Introduction

Available tools for schistosomiasis control are chemotherapy, health education, provision of safe water supplies, installation of adequate sanitation facilities and use of molluscicides for focal intermediate host snail control. However, the current aim of control is morbidity control and, chemotherapy is the most widely used strategy to achieve this goal (WHO 1993).

The most common method employed in diagnosing individuals and communities infected with urinary schistosomiasis has been detection and counting of eggs in urine. It is well acknowledged that this approach is time consuming, requires trained personnel and is thus expensive. A considerable amount of research has therefore been focused on the development and validation of rapid and low-cost diagnostic tools. The use of reagent sticks to detect proteinuria and microhaematuria have been employed for diagnosing urinary schistosomiasis

and have been shown to be reliable (Wilkins *et al.* 1979; Mott *et al.* 1985; Savioli *et al.* 1989; Lengeler *et al.* 1993; Mafe 1997). More recently, it has been investigated whether indirect screening tools, such as simple questionnaires, may be used to identify communities at highest risk of urinary schistosomiasis. The idea was to rely on committed personnel at the grassroot level and outside the health sector, but within a well established administrative system. The school system was identified as suitable with teachers interviewing their schoolchildren. The method was validated in several countries and its diagnostic performance was found to be good (Lengeler *et al.* 1991a, b; Red Urine Study Group1995; Ansell *et al.* 1997; N'Goran *et al.* 1998).

In Nigeria, schistosomiasis constitutes a public health problem particularly in children. Both *Schistosoma haematobium* and *S. mansoni* are present with the former being more widespread (Cowper 1973; Istifanus *et al.* 1988; Awogun 1990). Highest infection prevalences were observed among children aged 5-19 years who constitute 60-70% of all persons infected in the community (Cowper 1973; Tayo 1989). The distribution of schistosomiasis in the country is focal and at most times related to water development schemes, such as irrigation projects, rice/fish farming and dams.

Nigeria has a national schistosomiasis control programme that has the ultimate goal of eliminating schistosomiasis as a public health problem in the country. The age group 5-19 years has been defined as the target population for the nationwide control through the school system. Considering the focal nature of the disease, the vast terrain of Nigeria, the large size of population at risk and the limited resources for control, it is vital that communities at highest risk be identified to ensure that available control resources are utilised in the most effective way. The rapid identification of disease pockets in the endemic states of the nation will greatly define the control programme's actual needs and identify priority areas for intervention in a phased control programme. Donor agencies could also be attracted to take some of the responsibilities towards an effective and sustainable implementation of control measures.

The present report describes the development and validation of a questionnaire for rapid screening of communities at highest risk of *S. haematobium* infection in Borgu Local Government Area, Niger State. The design of the study also allowed to analyse the data on an individual level, since individual answers of the questionnaire could be related to individual parasitological results.

4.3   Materials and Methods

Study area

The study was conducted in Borgu Local Government Area (LGA), which is located in Niger State, north-western Nigeria (Figure 4.1), between March and December 1998. The total land area is 16,219 km^2 with a population estimated at 115,000 in 1994. Administratively, Borgu

LGA is divided into 10 districts of varying sizes and populations, with the headquarters located in New Bussa town. Major ethnic groups are Bissans, Bokkos, Laru, Gungawa, Lupawa and Nupe, each with their own distinct language. However, Hausa is the language spoken by most, while the predominant religion is Islam. Borgu LGA falls within the savannah zone, with annual rainfall of 1,000-1,200 mm. The Kainji Dam which is the largest man-made lake in the country was constructed in Borgu LGA between 1962 and 1968. The dam was built primarily for the generation of hydro-electric power, but it also serves as one of the major sources of freshwater fish in Nigeria. The main occupation of the predominantly rural population is farming, while along the lake shores, fishing and trading play major roles. Pipe-borne water and electricity are only to be found in and around New Bussa, while the rest of the LGA rely on boreholes, wells and surface water bodies. The road network is poor and access to remote villages during the rainy season is difficult. Most villages have one primary school, while in some cases a group of two or more villages share the same school. In total, there are 64 primary schools in the LGA, 60 of which were enrolled in the study.

Schoolchildren's questionnaire

Throughout the survey, the study was presented as a general health survey of the Borgu LGA with particular interest on school children's health. The questionnaire used by Lengeler *et al.* (1991a, b) was employed as an entry point in developing a discussion guide for focus group discussions (FGD). They were conducted following the manual provided by Dawson *et al.* (1992), and used to probe for local terms of urinary schistosomiasis. Two FGDs were held each with three different groups: (1) primary school children, (2) head teachers and (3) health staff. For each group one FGD was conducted with males only and the other with females only. The groups were representative with respect to ethnic groups, although as expected, with higher representation of Bissan, the main ethnic group in the LGA.

The original questionnaire was modified using the information obtained from the FGDs. The term 'bilharzia' was used instead of 'schistosomiasis' and its most common local term was '*fisari da jini*', which was inserted in bracket. Other terms were understood both in English and when translated in the main local languages: Hausa, Bissang or Yoruba. The questionnaire was pre-tested in two schools to ensure correct understanding by teachers and children. After pre-testing, FGDs were conducted in these two schools, with both interviewed children (total: 7, both sexes), and the teachers who carried out the interviews. It was found that no other modifications were necessary. The questionnaire can be obtained from the authors.

Figure 4.1
Map of the study area: Niger State, north-western Nigeria.

The questionnaires were accompanied by two separate forms according to a procedure already used in Côte d'Ivoire: (1) instructions for teachers and (2) blank class lists. First, the teachers were asked to read the instructions and then to fill-in the names (alphabetical order), sex and age of their pupils in the class list. After complete filling-in, children were interviewed individually, according to alphabetical order. Answers were recorded as: 'yes', 'no' and 'don't know' (counted as 'no' in the evaluation). This procedure allowed for data analysis at the individual level, since individual answers could be related to individual parasitological results.

Questionnaires were deposited at the office of the Education Secretary in New Bussa for delivery to the 60 primary schools. The head teachers of classes 3-5 interviewed their children individually in English and local languages. Completed questionnaires were expected to be returned to the office of the Education Secretary within 4 weeks, from where they were retrieved by the research team. Questionnaires were given prior screening to determine the return rate, the correctness of filling-in and to identify areas for clarifications before data entry.

Questionnaire validation: reagent stick testing by school teachers

All schools that returned correctly completed questionnaires were considered for biomedical validation. Letters were addressed to all head teachers of these schools inviting them to a one-day workshop. The objectives of the biomedical validation were explained and teachers were taught on how to test for microhaematuria by the use of reagent sticks (Sangur sticks, Boehringer Mannheim, Germany). It was emphasised that urine specimens should be collected only between 10:00 and 14:00 hours. Test results were classified into four categories according to the manufacturer's instructions and were recorded as negative, 1+, 2+ and 3+. At the end of the day, teachers were equipped with complete survey kits (copies of the listing sheets previously filled-in with an empty column to fill-in reagent stick test results, urine containers, gloves, reagent sticks, soap and plastic bucket). Head teachers confirmed that they would conduct the reagent stick tests as soon as possible and return their results within a maximum period of 4 weeks.

Evaluation of teacher's reagent stick testing and treatment of infected children

Our research team returned to 20 randomly selected schools and performed biomedical tests, using reagent sticks and standard urine filtration. Urine specimens were collected between 10:00 and 14:00 hours and they were first tested by reagent sticks, as explained above. Then, 10 ml of urine were filtered through Nucleopore paper filters. They were stained with a drop of Lugol and examined under light microscope for the presence and number of *S. haematobium* eggs. Results of this standard technique were considered as 'gold standard'. For those schools where at least 15 children were tested with both methods, a linear regression was drawn between the prevalence rate of *S. haematobium* (assessed by urine filtration) and the prevalence rate of microhaematuria at the 1+and 2+ positivity level (assessed by reagent stick testing).

All children with a positive reagent stick result obtained by the research team were directly treated with a single oral dose of praziquantel (under supervised administration) at the recommended standard dose of 40 mg per kg body weight (WHO 1993).

Data management and statistical analysis

All questionnaire and parasitological data were double-entered and cross-checked using EpiInfo software (version 6.04; Centres for Disease Control and Prevention, Atlanta, Georgia, USA). The diagnostic performance of reagent sticks was assessed by comparing with the results of urine filtration. Results of teacher's reagent stick testing were compared with those of the research team in order to assess the reliability of teacher's testing.

At the community (school) level, Spearman rank correlation was computed between the school infection prevalence of microhaematuria and the questionnaire positivity rates in each school. The diagnostic performance of the questionnaire to identify a school where the children are at highest risk of microhaematuria was calculated by computing the sensitivity, specificity and predictive values, including 95% confidence intervals. Logistic regression analysis was performed at the individual level for those children who had a reagent stick result and complete questionnaire answers, in order to assess the most reliable reported symptom(s) and/or disease(s) for individual diagnosis of *S. haematobium* infections.

4.4   Results

Focus Group Discussions

The terms 'bilharzia' and 'schistosomiasis' were unknown to the school children. However, local names were well known, in Hausa these are *'fisari da jini',* and '*boli da jini*', with the former more widely understood than the later; and in Bissanya the term is '*osoroku aruwo*'. The interpretation of these local names is 'blood in urine'. A large majority of the teachers were also unfamiliar with the terms 'bilharzia' and 'schistosomiasis'. The teachers however clearly understood the disease as passing of blood in urine although many of them did not know the cause. All the health staff were familiar with the two terms 'bilharzia' and 'schistosomiasis'. Blood in urine was well understood and the same local terms were given as stated above.

A few teachers and a few children also attributed the symptom of blood in urine to gonorrhoeal infection and sexually transmitted diseases. Similar observations were made for 'pain when urinating'. Consequently, such conditions were strongly linked to prostitution.

Operational results

The return rate of school questionnaires was high, with 58 out of the 60 schools (96.7%) returning correctly completed questionnaires within 4 weeks. A total of 3,033 children were interviewed individually by their teachers: 1,123 in class three, 956 in class four and 954 in class five. The mean age was 11.2 ± 2.1 years and the sex-ratio (male/female) was 1.9. An average of 52 children were interviewed per school (range: 3-457). Overall, 24.8% (95% confidence interval (CI): 23.3-26.4%) of the children responded positively to the question on excretion of blood in their urine during the last month and 24.1% (95% CI: 22.5-25.6%) said that they had had bilharzia.

Overall, 56/58 schools (96.6%) sent in their results of the reagent stick tests. One of the two schools that did not return the validation results had a fire accident that engulfed the school and its contents including the test documents and materials, while the second school claimed to have forwarded the results but these were never received. Teachers tested 2,479 children (mean: 44 per school, range: $3 - 327$). The mean age was 11.2 ± 2.1 years (range $5 - 23$ years) and the sex-ratio was 2.0. Prevalence rate for microhaematuria at 1+ positivity level was 43.7% (95% CI: 41.7-45.7%), and 27.1% (95% CI: 25.4-28.9%) at 2+ positivity level.

Validation of reagent stick testing

Cross-checking was performed on 529 children in 20 randomly selected schools (mean number of children per school: 27, range: $4 - 76$). Their mean age was 11.0 ± 1.8 years (range: $7 - 20$) and the sex-ratio was 2.1, therefore a population similar to the one interviewed by questionnaires and tested by the teachers with reagent sticks. A comparison of the filtration results with the results of the reagent stick testing, both obtained by the research team, gave good sensitivity and specificity values, as well as a good Kappa agreement (0.59 ± 0.04, $p < 0.0001$), showing the reliability of using reagent sticks (Table 4.1). Comparison between the reagent stick results obtained by the research team and the teachers gave good sensitivity and specificity values, and also a good Kappa agreement (0.71 ± 0.05, $p < 0.0001$), although they were done on average 3 months apart (Table 4.2). These findings indicate the reliability of teacher's reagent stick results for the validation of the children's responses to the questionnaires.

Table 4.1

Comparison between urine filtration (considered as reference) and reagent stick testing both performed by our research team.

		Urine filtration		
		+	−	**Total**
Reagent stick testing	+	134	61	**195**
	−	38	296	**334**
	Total	**172**	**357**	**529**

Sensitivity: 77.9% (95% CI: 70.8-83.7%); specificity: 82.9% (95% CI: 78.5-86.6%); positive predictive value: 68.7% (95% CI: 61.5-75.0%); negative predictive value: 88.6% (95% CI: 84.6-91.7%); kappa agreement: 0.59 ± 0.04 ($p < 0.0001$).

Table 4.2

Comparison between reagent stick testing performed by our research team (considered as reference) and school teachers.

		Research team		
		≥ 1+	negative	**Total**
School teachers	≥ 1+	146	34	**180**
	negative	31	275	**306**
	Total	**177**	**309**	**486**

Sensitivity: 82.5% (95% CI: 75.9-87.6%); specificity: 89.0% (95% CI: 84.8-92.2%); positive predictive value: 81.1% (95% CI: 74.5-86.4%); negative predictive value: 89.9% (95% CI: 85.8-92.9%); kappa agreement: 0.71 ± 0.05 ($p < 0.0001$).

Correlation between questionnaire results and teacher's reagent stick testing

Preliminary analysis of the data showed that very few children were interviewed and tested with reagent sticks in some schools. Those schools with the lowest number of children were removed gradually, and the analysis repeated at each step. This process revealed that schools with less than 15 children interviewed and/or tested with reagent sticks were less reliable in the correlation between the questionnaire positivity rate and school prevalence of microhaematuria. Therefore, only the 39 schools that had at least 15 children interviewed and tested by reagent sticks were used for final analyses. Spearman rank correlation showed highly significant associations between the overall school prevalence of microhaematuria and reported bilharzia and also reported blood in urine, making these two the best questions in the study

area. At microhaematuria positivity level of 1+, reported bilharzia resulted in a rho-value of 0.48 (p = 0.003), which was slightly higher than the one measured for reported blood in urine (rho: 0.47, p = 0.004). Stronger correlations were obtained at the 2+ positivity level of microhaematuria, for both reported blood in urine and reported bilharzia, with corresponding rho-values of 0.63 (p<0.001) and 0.59 (p<0.001), respectively.

The relationship between the overall school prevalence of microhaematuria at the 2+ level and the frequency of children with reported blood in urine and reported bilharzia is depicted in Figure 4.2.
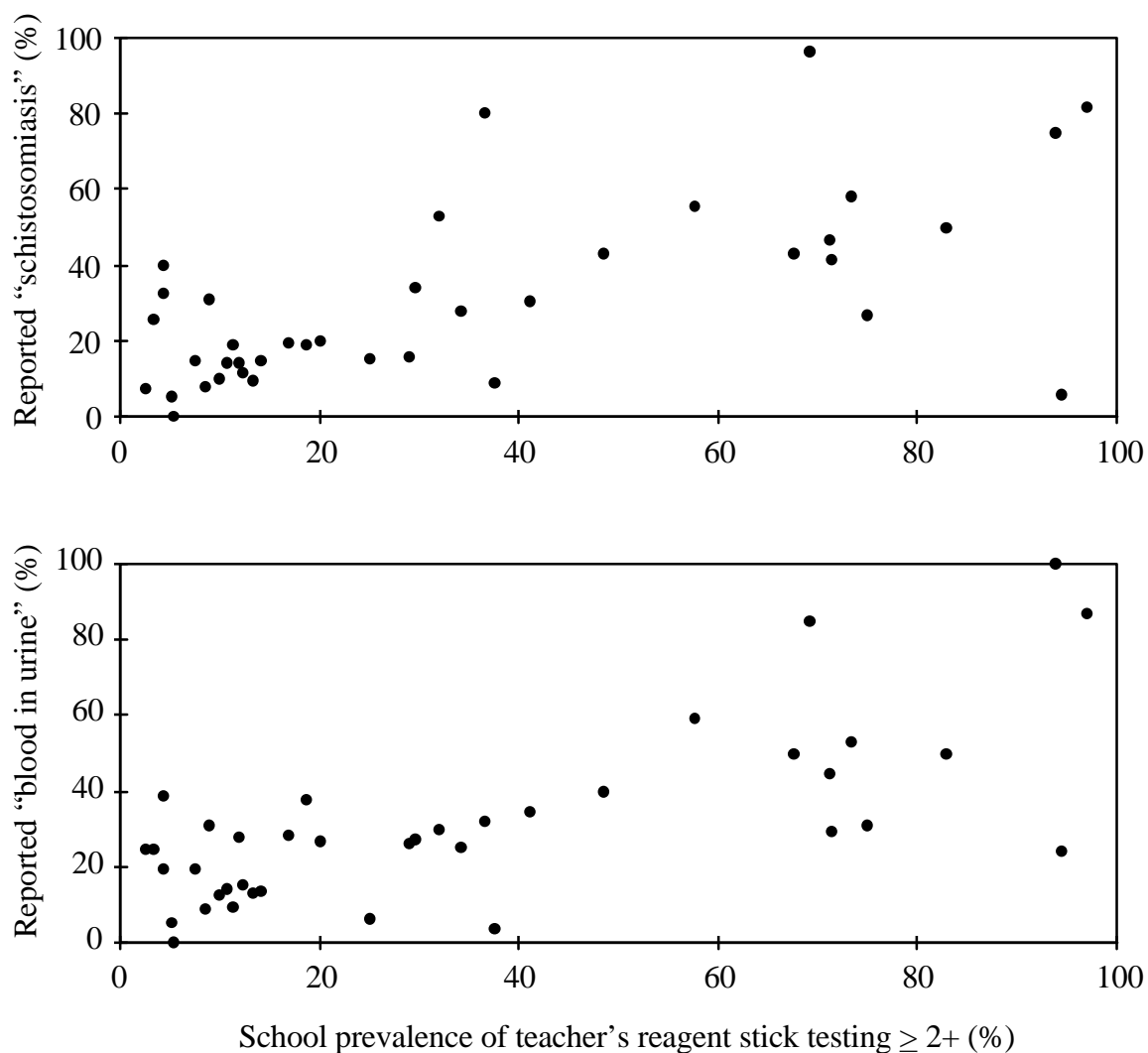
Figure 4.2

Relationship between school infection prevalence of microhaematuria ≥ 2+ and the prevalence of reported schistosomiasis (top) and reported blood in urine (below). Only those schools with ≥ 15 children interviewed and tested with reagent sticks were used for the analysis (n = 39).

Diagnostic performance of the questionnaire

In 13 schools more than 15 children were tested by our research team using standard urine filtration and reagent stick testing. The linear regression between the prevalence rate of *S. haematobium* (assessed by urine filtration) and the prevalence rate of microhaematuria (assessed by reagent stick testing) showed a significant correlation at both the 1+ and 2+ positivity level of microhaematuria, with the correlation at the 2+ level being higher than at the 1+ level. To compare the standard urine filtration screening method with the reagent stick testing results, the following linear transformation was computed:

Parasitological prevalence = 0.74 • prevalence of microhaematuria (≥ 2+) + 10.4

According to Montresor *et al.* (1998), parasitological prevalences of 20% and 50% can be considered as threshold for moderate or high school infection rates. The linear transformation resulted in prevalence rates for microhaematuria (≥ 2+) of 13.0 and 53.7%, respectively.

Consequently, the diagnostic performance of the questionnaire was calculated at these two detection thresholds of microhamaturia (≥ 2+). Both questions on reported schistosomiasis and reported blood in urine showed high sensitivities and specificities, especially at the high detection threshold. Of particular interest was the negative predictive value, i.e. a high negative predictive value permits the safe exclusion of schools where the risk of urinary schistosomiasis is low. At the high detection threshold, the negative predictive values were 90% and above for the two key questions (Table 4.3).

Table 4.3
Diagnostic performance of reported schistosomiasis and reported blood in urine at two different detection thresholds for reagent stick testing ≥ 2+ to detect schools with a high risk of urinary schistosomiasis (n = 39 schools).

	Questionnaire cut-off (%)	Diagnostic performance in % (95% CI)			
		Sensitivity	Specificity	PV+	PV-
Microhaematuria ≥ 2+: 13.0% (urine filtration: 20%)					
Reported bilharzia	15	72 (50-87)	64 (36-86)	78 (56-92)	56 (31-79)
Reported blood in urine	25	80 (59-92)	79 (49-94)	87 (65-97)	69 (42-88)
Microhaematiria ≥ 2+: 53.7% (urine filtration: 50%)					
Reported bilharzia	40	82 (48-97)	86 (66-95)	69 (39-90)	92 (73-99)
Reported blood in urine	40	73 (39-93)	96 (80-100)	89 (51-99)	90 (72-97)

So far, the relation between microhaematuria estimated with reagent sticks and the positive responses to reported blood in urine and reported schistosomiasis (bilharzia) has been constant in Africa. Linear regression analysis between previous findings from Tanzania (Lengeler *et al.* 1991b), eight other African countries (Red Urine Study Group 1995; N'Goran *et al.* 1998) and the present results from Nigeria show highly significant correlations between reported schistosomiasis and country microhaematuria ($\geq$ 1+) prevalence ($r = 0.90$, $p = 0.0003$; Figure 4.3a), as well as between reported blood in urine and country microhaematuria ($\geq$ 1+) prevalence ($r = 0.90$, $p = 0.0004$; Figure 4.3b).
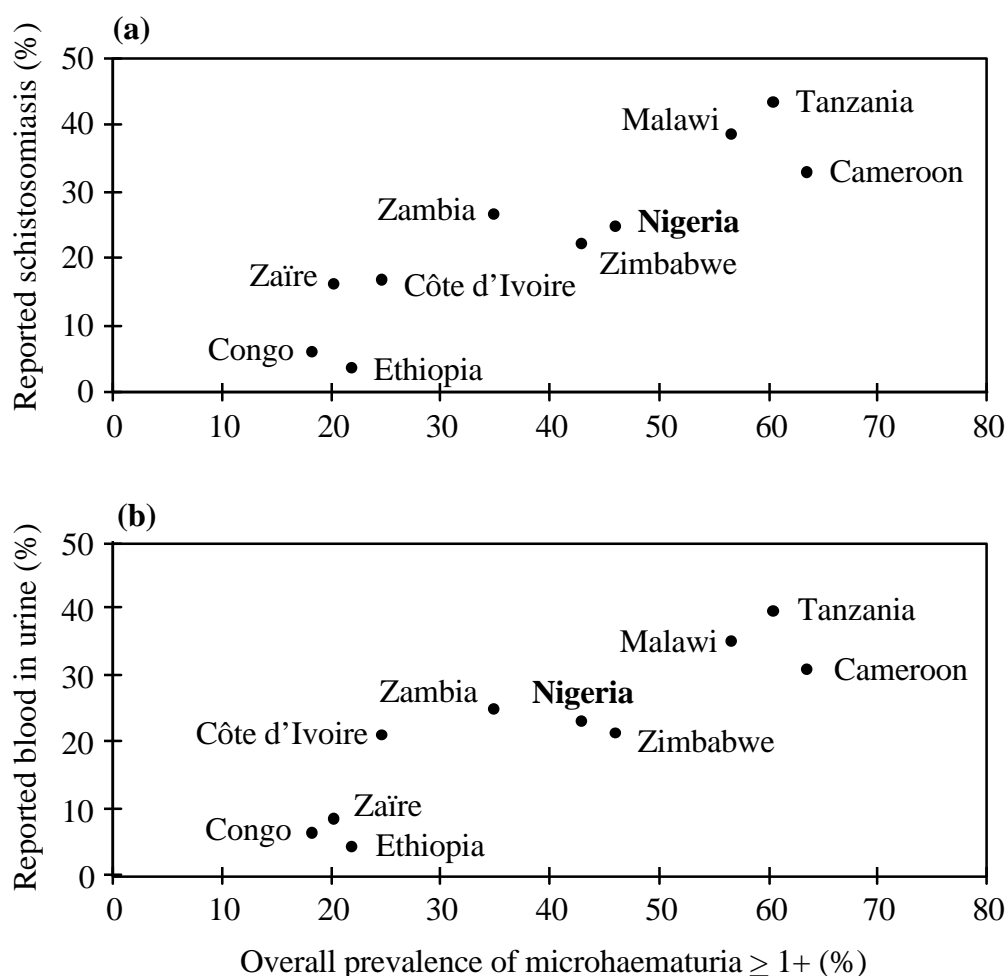
Figure 4.3

Review of all country studies to assess the relationship between the cumulative school infection prevalence of microhaematuria ($\geq$ 1+) and the prevalence of reported schistosomiasis (a) and reported blood in urine (b). Data sources: Tanzania: Lengeler *et al.* 1991b; Côte d'Ivoire: N'Goran *et al.* 1998; **Nigeria**: our data; other countries: Red Urine Study Group 1995.

Analysis at the individual level

Teacher's reagent stick testing results, as well as complete answers to the questionnaire were obtained from 2,378 children. The frequency of reported blood in urine and reported bilharzia increased significantly with increasing intensity of infection (Figure 4.4). Chi square test for linear trend revealed very high values of 222.9 (p < 0.0001) for reported blood in urine and 217.8 (p < 0.0001) for reported schistosomiasis.
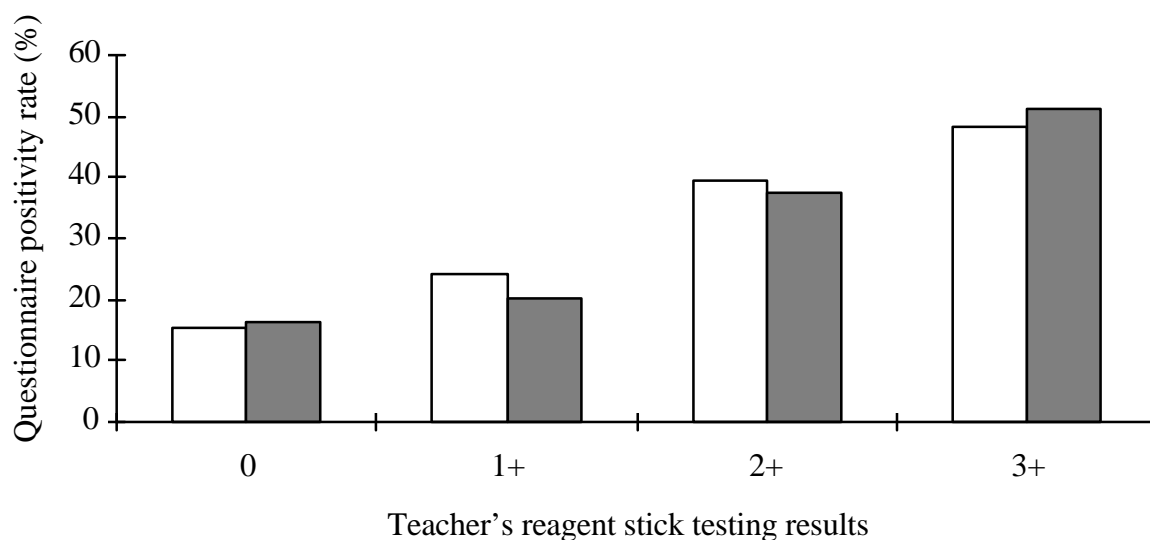
Figure 4.4
Percentage of children who reported having had schistosomiasis (white bars) and blood in urine (grey bars) during the last month in relation to intensity of reagent stick testing results.

Logistic regression analysis at the individual level showed that an infection with *S. haematobium* (microhaematuria ≥ 1+) was significantly associated with sex (adjusted odds ratio 0.74, 95% CI: 0.61-0.89, p = 0.001), indicating that girls were more likely to be infected. There was also a significant association with age (adjusted odds ratio 1.08, 95% CI: 1.04-1.13-, p < 0.001), with older children more often infected. Multivariate analysis revealed significant odds ratios for reported bilharzia and reported blood in urine. The adjusted odds ratios were 2.55 (95% CI: 1.99-3.25, p < 0.001) and 1.95 (95% CI: 1.54-2.48, p < 0.001), respectively (Table 4.4). At the 2+ positivity level of microhaematuria, the adjusted odds ratios for these two questions were higher with 2.91 (95% CI: 2.36-3.94, p < 0.001), and 3.05 (95% CI: 2.36-3.94, p < 0.001), respectively.

Table 4.4

Multivariate analysis to assess the best reported symptoms and/or diseases for identification of individuals with a reagent stick result of ≥ 1+ or ≥ 2+, after adjusting for confounding factors (n = 2,378 children).

Variable	Reagent stick results ≥ 1+		Reagent stick results ≥ 2+	
	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Children surveyed				
Age	1.08 (1.04-1.13)	< 0.001	1.10 (1.05-1.15)	< 0.001
Sex	0.74 (0.61-0.89)	0.001	0.74 (0.60-0.92)	0.007
Reported symptoms and/or diseases				
Bilharzia	**2.55 (1.99-3.25)**	**< 0.001**	**2.91 (2.36-3.94)**	**< 0.001**
Blood in urine	**1.95 (1.54-2.48)**	**< 0.001**	**3.05 (2.36-3.94)**	**< 0.001**
Cough	**0.71 (0.59-0.85)**	**< 0.001**	**0.74 (0.59-0.92)**	**0.006**
Malaria	**0.78 (0.64-0.94)**	**0.008**	**0.77 (0.61-0.95)**	**0.017**
Diarrhoea	**1.27 (1.04-1.54)**	**0.019**	0.94 (0.74-1.18)	0.573
Intestinal worms	**0.80 (0.66-0.98)**	**0.029**	**0.76 (0.60-0.95)**	**0.018**
Vomiting	0.86 (0.71-1.04)	0.120	**0.73 (0.59-0.92)**	**0.006**
Blood in stool	0.92 (0.74-1.13)	0.421	**0.71 (0.55-0.91)**	**0.006**

4.5 Discussion

Towards the end of the 1980s, Lengeler *et al.* (1991a) presented a simple questionnaire that allowed rapid identification of communities at highest risk of *S. haematobium* infection in a rural Tanzanian district. Questionnaires were administered through the existing school system and found to be feasible and effective. The method was first validated in a neighbouring district (Lengeler *et al.* 1991b), and then in seven other African countries: Cameroon, Congo, Democratic Republic of Congo (formerly Zaïre), Ethiopia, Malawi, Zambia and Zimbabwe (Red Urine Study Group 1995). Most recently, the questionnaire was validated in another Tanzanian district (Ansell *et al.* 1997), in Côte d'Ivoire (N'Goran *et al.* 1998) and is currently under validation in Guinée (P. Winch & M. Murray, personal communication). So far, with only the exception of Ethiopia (Jemaneh *et al.* 1996), highly significant correlations were found between the proportion of children with reported schistosomiasis, as well as reported blood in urine, and the proportion of children infected with *S. haematobium*.

In view of these findings, it was concluded that questionnaires are rapid, easy to perform, reliable, non-intrusive and highly cost-effective to screen for *S. haematobium*. However, it was suggested to carry out further validation when significant changes have been made to the

questionnaire or where strong arguments are needed to convince health authorities about the usefulness of the method (Chitsulo *et al.* 1995). In the case of Nigeria, these two reasons were met. Although the original questionnaire provided by Lengeler *et al.* (1991a, b) was used as an entry point, it was considerably modified, following a series of focus group discussions conducted with school children, head teachers and health staff. Questionnaires were considered a promising tool for rapid identification of priority areas for schistosomiasis control in Nigeria, so that limited resources of the national programme can be used most effectively. A validation of questionnaires was therefore necessary to provide sound recommendations about the potential large scale application of this method.

The design of the questionnaire validation used in the present study followed that of previous surveys. In a first step, questionnaires were modified, pre-tested, finally adapted and then administered through the existing school system. Novel in our approach was, that questionnaire modifications were carried out on the basis of several focus group discussions. This procedure was effective and allowed for rapid identification of common local terms for passing blood in urine. Focus group discussions were also successfully used in Côte d'Ivoire to determine common symptoms and local terms to predict an infection with *S. mansoni* (Utzinger *et al.* 1998), as well as an infection with *Entamoeba histolytica/E. dispar* (Utzinger *et al.* 1999).

In a second step, questionnaires were validated with reagent stick tests performed by previously trained teachers. Validation by teachers had already been reported from Tanzania (Lengeler *et al.* 1991b), and from eight other African countries (Red Urine Study Group 1995; N'Goran *et al.* 1998). In summary, teacher's performance and commitment was excellent and they consistently stated, that they have been proud having received training on the use of reagent sticks. Recently, it was suggested that teachers could play an important role in schistosomiasis control programmes (Magnussen *et al.* 1997), which we would like to support strongly.

In a third step, a biomedical team was sent to a random sample of schools to check the teacher's results by performing urine filtration and reagent stick tests. When the research team's results of the urine filtration were compared with those obtained from reagent stick testing, high sensitivity (78%) and high specificity (83%) were obtained. This is in good agreement with previous studies (Wilkins *et al.* 1979; Mott *et al.* 1983; N'Goran *et al.* 1989; Savioli *et al.* 1989; Lengeler *et al.* 1993; Mafe 1997). Comparison of the reagent stick results between the research team and the teachers also showed high sensitivity (83%) and high specificity (89%). Therefore, teachers' reagent stick results were a reliable means for biomedical validation of school questionnaires.

In view of our findings, it can be summarized that the present work, which is the first of its kind conducted in Nigeria, is in full agreement with previous results obtained from nine other African countries. It further supports the use of questionnaires for rapid screening of *S. haematobium*. It was interesting to note, that the two key questions of reported blood in

urine and reported schistosomiasis showed better correlations with the 2+ level of microhaematuria than with the 1+ level. This was also observed by Lengeler *et al.* (1991b), but is in disagreement with Lwambo *et al.* (1997).

However, there is one major concern which represents a serious issue in the present study. It is the school enrolment which was found to be very low in several of the schools surveyed. For final analysis, schools with less than 15 children interviewed or tested with reagent sticks were removed, which represented a high percentage of the schools (30%). Removing schools for statistical analysis is defensible, to recommend such an approach to schistosomiasis control managers is however unacceptable. Further more, as it was observed that several of the schools removed had very high prevalences of microhaematuria. It may be proposed that in schools with only few children, all of them, instead of only classes 3-5, should be interviewed.

We believe that our survey contains an additional element which is novel and clearly merits space for discussion. Questionnaires were accompanied by blank class lists, and teachers were asked to fill-in these forms prior to individual interviewing of the children. For data analysis, this enabled the determination of the diagnostic performance of the questionnaire not only on school but also on individual level. This idea was recently developed in Côte d'Ivoire and it was found to be well understood by teachers as they followed the instructions correctly. Logistic regression modelling revealed significant odds ratios for reported schistosomiasis and reported blood in urine. However, at the 1+ level of microhaematuria the adjusted odds ratios were rather low: 2.55 and 1.95 for these two key questions, respectively. In a previous study in Tanzania, reported blood in urine showed a much higher adjusted odds ratio of 7.71 (Booth *et al.* 1998). At the 2+ positivity level of microhaematuria, the adjusted odds ratios were considerable higher: 2.91 and 3.05, respectively. Another study conducted in Tanzania revealed that self-reported schistosomiasis was a valuable indicator to identify infected individuals, especially in those schools with a high infection prevalence (Ansell *et al.* 1997). In light of these results, it seems advisable to further investigate whether questionnaires could also be used for individual diagnosis of *S. haematobium*, as is also suggested by Barreto (1998).

4.6 Acknowledgements

4.7 References

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5   *Schistosoma mansoni,* **intestinal parasites and perceived morbidity indicators in schoolchildren in a rural endemic area in western Côte d'Ivoire**

J. Utzinger [1,2], E.K. N'Goran [2,3], C.M. Esse Aya [4], C. Acka Adjoua [4], K.L. Lohourignon [3], M. Tanner[1], C. Lengeler[1,$]

1   Swiss Tropical Institute, Department of Public Health and Epidemiology, PO Box, CH-4002 Basle, Switzerland

2   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

4   Département de Sociologie, Université de Cocody, 22 BP 3555, Abidjan 22, Côte d'Ivoire

$ Corresponding author
     Tel: + 41 61 284 8221
     Fax: + 41 61 271 7951
     e-mail: christian.lengeler@unibas.ch

5.1 Summary

There exists a great need for rapid and low-cost identification of communities at high risk of intestinal schistosomiasis. We report the development of a questionnaire approach that may do so. In a first phase, 209 schoolchildren from three neighbouring villages in a rural area endemic for intestinal schistosomiasis in western Côte d'Ivoire were screened for *Schistosoma mansoni* and other helminths on four consecutive days, using Kato-Katz thick smears. Daily infection prevalences of *S. mansoni* were high (60% - 71%) and the cumulative infection prevalence was 92.3%. Infections with hookworms and *Ascaris lumbricoides* were also frequent, with cumulative prevalences of 60.8% and 38.3%, respectively. On day 3, the presence of *Entamoeba histolytica/E. dispar* and *Giardia lamblia* was assessed by a faecal concentration procedure. In a second phase, focus group discussions (FGD) were conducted: in each village one FGD with heavily infected children and one FGD with non or lightly *S. mansoni* infected schoolchildren to assess their perception of morbidity. The aim was to establish local terms indicating *S. mansoni* infections. 'Diarrhoea', 'blood in the stools', 'stomach disorders' and 4 terms in the local Yacouba/Dioula languages were frequently reported among infected children. A simple questionnaire was then developed and the headteachers interviewed all schoolchildren individually. It was found that 'blood in stools', '*gnon*' and '*toto*' were reported significantly more frequently among moderately and heavily *S. mansoni*-infected children when compared with those not or only lightly infected. The term '*gloujeu*' showed borderline significance. The best diagnostic performance was found for 'blood in stool' (sensitivity: 47%; specificity: 76%; positive predictive value: 66%; negative predictive value 60%). All schistosomiasis infections were treated with a single oral dose of praziquantel (40 mg per kg body weight) and the same questionnaire was re-administered 6 weeks post-treatment. Statistically significantly less children reported having had 'blood in stool' and '*gloujeu*' after treatment (McNemar chi-squared test, $p < 0.01$). It is concluded that 'blood in stool', '*gnon*', '*toto*' and '*gloujeu*' are the most reliable reported symptoms for rapid and low-cost identification of communities that are at high risk of *S. mansoni* infections in the Côte d'Ivoire.

Key words: Côte d'Ivoire – Intestinal schistosomiasis – *Schistosoma mansoni* – Intestinal parasites – Morbidity – Disease perception – Rapid assessment procedures

5.2 Introduction

It is well established that the distribution of schistosomiasis is focal (Webbe & Jordan 1993) and that it is essential to target control activities to high risk areas. This clearly emphasises the relevance and need of rapid assessment procedures which are able to determine rapidly, at low-costs but accurately, whether the community of a certain area is at risk or not (Vlassoff & Tanner 1992).

For urinary schistosomiasis a simple schoolchildren questionnaire proved to be very successful for the identification of high risk communities in several African countries (Lengeler *et al.* 1991, Lengeler *et al.* 1992, Red Urine Study Group 1995, N'Goran *et al.* 1998). There is a clear need to develop a similar questionnaire approach for intestinal schistosomiasis but this may be difficult, as the signs and symptoms indicating such an infection show lower sensitivities and specificities than "blood in urine" for urinary schistosomiasis. However, preliminary work carried out in Zaire (Red Urine Study Group 1995) and in Ethiopia (Hailu *et al.* 1995) suggested that such a community diagnosis approach might be feasible. A recent study in Tanzania confirmed this (M. Booth & C. Mayombana personal communication).

Several community- and hospital-based studies have been carried out to assess the morbidity of intestinal schistosomiasis due to *Schistosoma mansoni* and to evaluate different signs and symptoms with regard to their diagnostic performance in predicting infection and/or morbidity. For most areas of sub-Sahara Africa, significant associations exist between *S. mansoni* infections and the presence of diarrhoea, especially bloody diarrhoea and/or blood in the stool (Arap Siongok *et al.* 1976, Hiatt 1976, Omer *et al.* 1976, Hiatt *et al.* 1977, Abdel-Wahab *et al.* 1980, Sukwa *et al.* 1985, Sukwa *et al.* 1986, Gryseels & Poldermann 1987, Gryseels 1988, Gryseels & Nkulikyinka 1990, Gryseels & Poldermann 1991, Kardorff *et al.* 1997). In his review of the literature, Gryseels (1992) stated that abdominal pain and colicky cramps were also found to be associated with *S. mansoni* infections. For the signs and symptoms listed above the relationship with intensity of infection is often rather good at community level but not at individual level (see review by Gryseels & Poldermann 1991). In view of these findings, it was proposed that such symptoms could be of use for diagnostic purposes, especially where no laboratory facilities are available (Sukwa *et al.* 1985, Lima e Costa *et al.* 1991).

A recent study undertaken in Zambia however could not demonstrate any association between one of the above symptoms and an infection with *S. mansoni* (Mungomba & Kalumba 1995). Proietti & Antunes (1989) also did not find significant differences between infected and non-infected groups in Brazil, and Prata (1982) stated that a variety of abdominal symptoms are not necessarily associated with *S. mansoni*. In addition, the presence of other gastrointestinal infections, such as hookworms, may contribute to the same symptoms (Sukwa *et al.* 1985, Lima e Costa *et al.* 1991). Some of these discrepancies could be explained by the fact that the "true infection prevalence" of *S. mansoni* is considerably underestimated when only one stool specimen is collected instead of repeated ones over at least three consecutive days (De Vlas & Gryseels 1992, De Vlas *et al.* 1993, Engels *et al.* 1996).

Little is known about school children's perception of the morbidity caused by *S. mansoni* and no such investigations have been undertaken before in West Africa. The importance of understanding and focusing on perceived morbidity in view of planning morbidity control (as opposed to infection control) is clear, and the need for rapid assessment procedures should be seen in the context of the high variability of described morbidity in different places in the world (Gryseels 1992). The present study was designed with four main aims. Firstly, to investigate the infection status for *S. mansoni* and other gastrointestinal parasites among schoolchildren

attending standard 4-6 in three primary schools in a schistosomiasis-endemic area of western Côte d'Ivoire by screening on four consecutive days. Secondly, to carry out focus group discussions with schoolchildren very heavily or not/very lightly infected with *S. mansoni* to assess their morbidity perception and probe for local terms that may describe the disease. Thirdly, to quantify the sensitivity, specificity and predictive values of different signs and symptoms that may be used for a rapid and low-cost screening of *S. mansoni* foci. Fourthly, to re-assess the morbidity perception of children 6 weeks after treatment.

5.3   Materials and Methods

Study area

The study was conducted in three primary schools of the neighbouring villages of Gueupleu, Gbatongouin and Mélapleu, located some 15 to 25 km north-west of Man, in western Côte d'Ivoire (Figure 5.1). Village houses have walls of mud or bricks, and are roofed with grass thatch or corrugated iron. Villagers are mainly engaged in subsistence farming, with rice and manioc as predominant crops. The mean annual precipitation is 1,600 mm (N'Goran *et al.* 1989). The climate in this area is characterized by rains during 8-9 months of the year, with a dry spell between November and February. Intestinal schistosomiasis is endemic in the village of Gueupleu, where 60% of the population were found to be infected in 1989 (N'Goran *et al.* 1989). No previous information was available for the two neighbouring villages, but intestinal schistosomiasis was among the most diagnosed diseases in the local dispensary in Gbatongouin (without laboratory confirmation and with unclear diagnostic criteria).

Schistosomiasis and other intestinal parasites

A total of 241 schoolchildren attending standard 4-6 were enrolled in the study. The sex and age of each subject were recorded and stool specimens were collected over five consecutive days. Since a large number of children did not provide all five specimen the analysis was subsequently restricted to four samples given on any of the five days. Plastic containers (volume 125 ml) were distributed to all the subjects and they were asked to provide a small portion of their morning stools. In order to assess whether *S. haematobium* was present in the study area, urine specimens were also collected on the same five consecutive days, always between 10.00 and 13.00 hours. They were directly analysed for the presence of microhaematuria, using reagent sticks (Sangur-Test, Boehringer Mannheim, Germany). According to the manufacture's instructions, testing results were classified into four categories: negative, 1+, 2+ and 3+. Only testing results of $\geq 2+$ were considered for quantifying point prevalence, as this level is more clearly related to schistosomiasis morbidity.
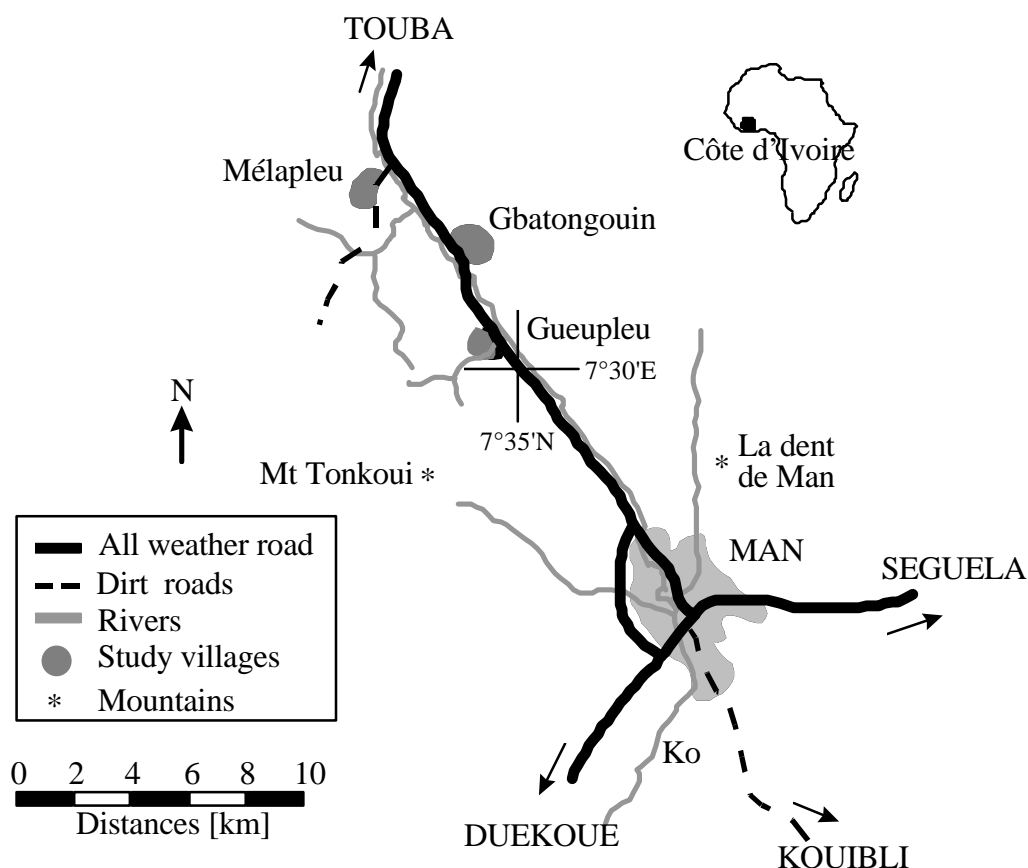
Figure 5.1

Map of the study area with the three villages in western Côte d'Ivoire where all school children attending standard 4-6 were screened for *Schistosoma mansoni* and other intestinal parasites.

Stool specimens were brought to the central laboratory in Man and first examined macroscopically, recording the degree of moisture and whether mucus or blood were present, according to WHO (1991). From each stool sample, a single 42 mg Kato-Katz thick smear was processed as described by Katz *et al.* (1972). The slides were examined quantitatively within 30 to 150 minutes after preparation by one of four experienced technicians, counting all the eggs of *S. mansoni*, hookworms, *Ascaris lumbricoides* and *Trichuris trichiura*. As quality control, 10% of the slides were randomly selected and rechecked for *S. mansoni* eggs by one senior technician. The time lag between preparation of the slides and reading was not optimal for hookworm eggs because they are more fragile and they are at risk of being destroyed after an hour on the slide.

On day 3, an additional portion of stool was preserved in sodium acetate-acetic acid-formalin (SAF) and processed according to Marti and Escher (1990), for the diagnosis of pathogenic protozoa, such as *Entamoeba histolytica/E. dispar* and *Giardia lamblia*. The samples were forwarded to a reference laboratory in Switzerland and analysed within 2 months.

Focus group discussions

Focus group discussions were conducted following the manual provided by Dawson *et al.* (1992). During the initial training of the interviewers, a first question-line to assess the perception of morbidity due to intestinal schistosomiasis was developed. It was pre-tested in the study area with a group of eight schoolchildren highly infected with *S. mansoni*, who were not enrolled in further studies. Subsequently, the question-line was finalized and two focus group discussion with 8 children were conducted in each village. One group consisted of heavily *S. mansoni* infected children, the other group of not or only very lightly infected children (less than 25 eggs per gram stool). The interviewers carrying out the focus group discussions were unaware of the parasitological results of the group participants.

School children's questionnaire

Based on the results of the focus group discussions, a simple questionnaire was developed. It consisted of questions of three main categories: (i) potential signs and symptoms that may indicate a *S. mansoni* infection, (ii) common terms for these signs and symptoms in the local Yacouba/Dioula languages and (iii) health seeking behaviour when such symptoms occur. The teachers in the different classes interviewed all the schoolchildren individually. The questionnaire was administered on two occasions: before, and 6 weeks after treatment against schistosomiasis.

Treatment of infected schoolchildren

All children who showed at least one *S. mansoni* egg in any of the five stool specimens were treated with a single oral dose of praziquantel at the recommended standard dose of 40 mg per kg body weight (WHO 1993). This treatment was given immediately after the questionnaire was administered for the first time. Six weeks later, the schoolchildren's questionnaire was re-administered for the second time and this was followed by treatment of those children with eggs of hookworms and *A. lumbricoides*, using two oral doses of pyrantel (10 mg per kg body weight), given within 15 days.

Data management and statistical analysis

All parasitological and questionnaire data were double-entered and validated using EpiInfo software (version 6.04; Centres for Disease Control and Prevention, Atlanta, Georgia, USA). For further analysis, only those children with at least four stool samples and complete answers to the questionnaire were included. All analysis were done at individual level. The arithmetic mean of egg output from the four stool samples was calculated and used for the classification of the infection status. Univariate statistics were used to assess the effect of infection status with regard to age, sex and village. Potential confounding by other intestinal parasites was assessed by logistic regression modelling, using EGRET software (Statistical and Epidemiology Research Corporation and Cytel Software Corporation, Seattle, WA 98105, USA). Logistic regression modelling was used to assess the odds ratio (including 95%

confidence intervals) for different signs and symptoms as predictors for *S. mansoni* infections. Sensitivity, specificity and predictive values were then calculated to assess the diagnostic performance of the most promising signs and symptoms. Questionnaire results of moderately or heavily infected children were compared before and after treatment, using McNemar's chi-squared test.

5.4   Results

Operational results

From the 241 schoolchildren enrolled in the study, at least four stool specimens as well as complete responses to all questions from the initial questionnaire were obtained from 209 children (86.7%). The mean age of the 209 schoolchildren was 12.4 years (range 8-16 years) and the male/female ratio was 1.82. The mean age of boys (12.6 years, range: 8-15) was slightly higher than that of girls (12.0 years, range: 9-16; Kruskal-Wallis H = 8.71, p = 0.003).

Occurrence of intestinal parasites

S. mansoni was the most frequently observed intestinal parasite. Day-to-day point prevalences of infection ranged between 59.8% and 70.8% and resulted in a cumulative infection prevalence of 92.3% after four days. Daily prevalence rates of infections with more than 100 eggs per gram stool (epg), ranged between 34.4% and 42.1%, with a cumulative prevalence of 49.3% (Tables 5.1 and 5.2). *S. mansoni* infection status was classified into four classes: (i) no infection; (ii) light infection: 1-100 epg; (iii) moderate infection: 101-400 egp and (iv) heavy infection: > 400 epg. There was no significant association between infection status and sex (χ^2, 3 degrees of freedom (d.f.) = 3.34, p = 0.34); age (χ^2, 9 d.f. = 7.82, p = 0.55) and village (χ^2, 6 d.f. = 10.09, p = 0.12). Therefore, the data were pooled for further analysis.

Infections with hookworms and *A. lumbricoides* were also observed frequently: the cumulative infection prevalences were 60.8% and 38.3%, respectively, although the prevalence rate for hookworms is likely to be under-estimated (Table 5.2). Intensities of infections were low for those helminths (only 2 children with a hookworm egg output of more the 1,000 per gram stool and only 2 children with an *A. lumbricoides* egg output of more than 5,000 per gram stool. Eggs of *T. trichiura* were only found in 4 children (1.9%). A total of 11 children (5.3%) had at least one reagent stick result of ≥ 2+ over the four days, indicating that *S. haematobium* infections were rare in the study area. As infections with *T. trichiura* and *S. haematobium* were rare, they were not considered for further analysis. Examination of the SAF fixed stool samples from a single day revealed point prevalences of the two pathogenic protozoa *E. histolytica/dispar* and *G. lamblia*, of 37.3% and 12.0%, respectively.

Table 5.1

Daily fluctuations of *Schistosoma mansoni* egg output, as assessed by single 42 mg Kato-Katz thick smears (n = 209). epg = egg per gram stool.

		Number of children according to infection status			
		Day 1	Day 2	Day 3	Day 4
Infection status (epg)					
Negative	(0)	79	84	73	61
Light infection	(1-100)	46	46	64	60
Moderate infection	(101-400)	59	56	48	45
Heavy infection	(> 400)	25	23	24	43
Daily prevalence		62.2%	59.8%	65.1%	70.8%
Daily intensity > 100epg		40.2%	37.8%	34.4%	42.1%

Multiple infections were common in the study area and the different combinations of *S. mansoni* infections with other intestinal parasites is given in Figure 5.2. It was found that 57.4% of the children were both infected with *S. mansoni* and hookworms, 36.4% with *S. mansoni* and *E. histolytica/E. dispar* and 35.9% with *S. mansoni* and *A. lumbricoides.* Infections with three parasites were also recorded frequently and in the faeces of two children we found five different pathogenic intestinal parasites.

Results of the focus group discussions

It was interesting to note that, although the interviewers in the focus group discussions were unaware of the parasitological results of the group participants, they always correctly identified the infection status of the group when they were asked at the end. Hence it was expected that the signs and symptoms given by the group of heavily infected children would be reported more frequently by such children when they were interviewed individually. The most common signs and symptoms that were given by the heavily infected children were the following: 'blood in stool', 'diarrhoea' and different local expressions for abdominal disorders. A 13 years-old boy said the following: "the stool is just like water and there is blood inside". Another boy (14 years) elaborated the following: "you have abdominal pain and you seek the latrine 9-10 times per day. You feel very tired and you have a general discomfort".

Less frequently, the disease 'schistosomiasis' was also stated. However, when the children were asked to elaborate on this term, not much additional information was obtained. It seemed that this was only a 'technical term' that they had picked up mainly in the school, without having a clear concept of it. Probing for common terms in the local Yacouba/Dioula languages that may explain the signs and symptoms given above, the children stated the following: '*kochleu*' (Yacouba: schistosomiasis); '*toto*' (Dioula: dysentery); '*gnon*' (Yacouba: blood) and '*gloujeu*' (Yacouba: (watery) diarrhoea eventually accompanied by the occurrence of mucus).

Most of the time, the group started laughing when they were asked to state these terms, which they explained by the fact that they were not allowed to use their local languages at school.

All children are seeking health advice from their mothers first. As expressed by a 10 years old girl: "When I have diarrhoea, I go to my mother and tell her about. She takes some leaves of a mango tree and boils them. I have to drink it and after that she washes me with black soap". The help of a doctor is only asked at a later stage, when the traditional treatment remains unsuccessful. "If it doesn't get better, I tell my mother and she brings me to the hospital. There, the doctor looks at my stool and gives me some pills afterwards" (boy, 13 years).

Table 5.2
Cumulative infection prevalences of *Schistosoma mansoni*, hookworms and *Ascaris lumbricoides* as assessed by the arithmetic mean of egg counts in stools over four days (n = 209). epg = egg per gram stool.

		Number of children according to infection status			
		Day 1	Day 2	Day 3	Day 4
Schistosoma mansoni					
Infection status (epg)					
Negative	(0)	79	43	21	16
Light infection	(1-100)	46	75	92	90
Moderate infection	(101-400)	59	68	76	72
Heavy infection	(> 400)	25	23	20	31
Cumulative prevalence		62.2%	79.4%	90.0%	92.3%
Cumulative intensity > 100epg		40.2%	43.5%	45.9%	49.3%
Hookworms					
Infection status (epg)					
Negative	(0)	130	112	91	82
Light infection	(1-1000)	75	94	116	125
Moderate infection	(1001-5000)	4	2	2	2
Heavy infection	(> 5000)	0	1	0	0
Cumulative prevalence		37.8%	46.4%	56.5%	60.8%
Ascaris lumbricoides					
Infection status (epg)					
Negative	(0)	169	150	140	129
Light infection	(1-5000)	38	57	67	78
Moderate infection	(5001-50000)	2	2	2	2
Heavy infection	(> 50000)	0	0	0	0
Cumulative prevalence		19.1%	28.2%	33.0%	38.3%
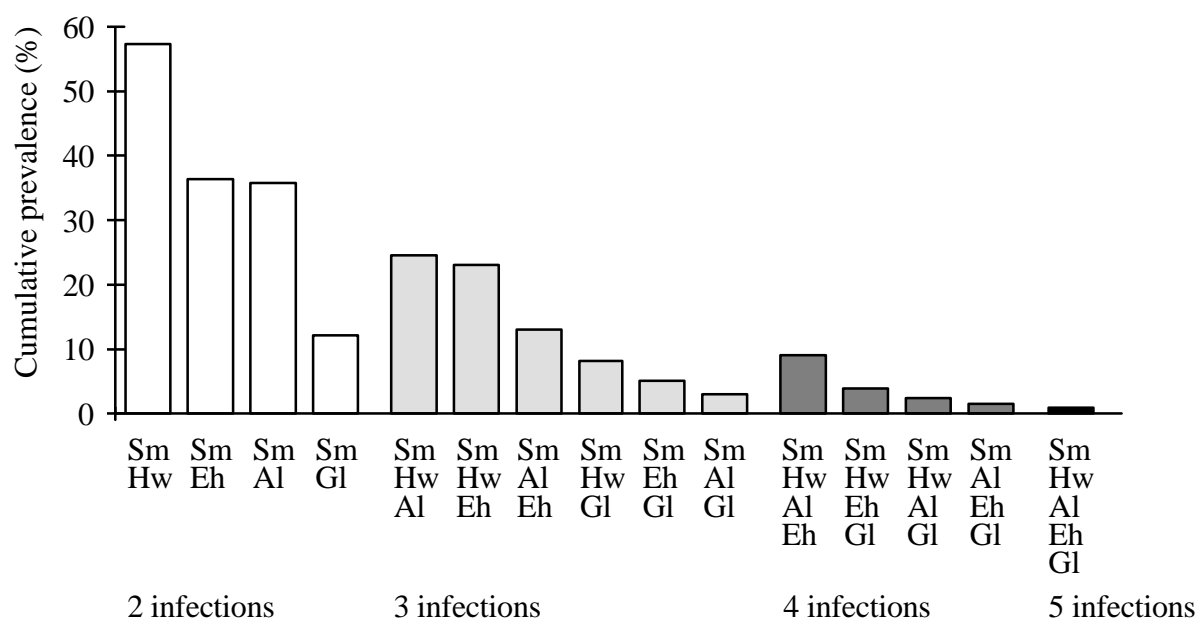
Figure 5.2

Cumulative prevalence of multiple infections among all the 209 children that were screened for *Schistosoma mansoni* (Sm), hookworms (Hw) and *Ascaris lumbricoides* (Al) on four days, as well as for *Entamoeba histolytica/E. dispar* (Eh) and *Giardia lamblia* (Gl) on a single day.

Association between S. mansoni infection and positivity rate of questionnaire

The signs and symptoms, as well as the common local terms in the Yacouba/Dioula languages derived from the focus group discussions were incorporated into the schoolchildren's questionnaire (that was applied by teachers). Neither the children nor the teachers were aware of the parasitological findings. Overall, 19 different questions were asked. Copies of the questionnaire are available from the authors on request.

For the sign 'blood in stool', the Yacouba term, '*gnon*' and the Dioula term '*toto*', clear associations were found between the questionnaire positivity rates and the different intensities of *S. mansoni* infections (Figure 5.3). An increasing egg output resulted in an increase of the positive answers to these three questions. Furthermore, there was a distinct cut-off at the level of 100 epg, indicating that children's disease perception changed at this level of infection. This is in good agreement with WHO (1993), setting the cut-off between light to moderate infections at 100 epg. This finding was taken into account for further analysis and thereafter only two groups were used: children with no or light infections (0-100 egp) and children with moderate to heavy infections (> 100 epg).
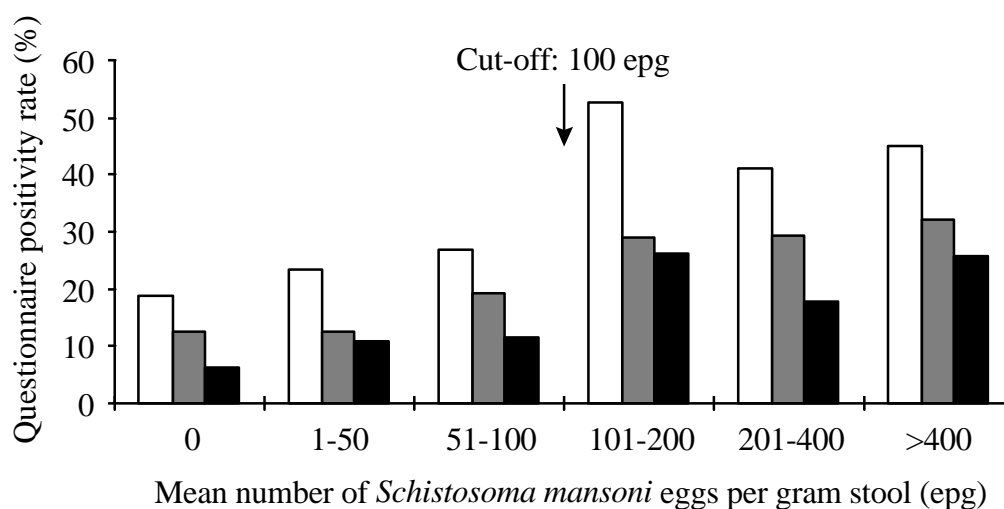
Figure 5.3

Children's perception of having had 'blood in stool' (white bars), '*gnon*' (grey bars) and '*toto*' (black bars) during the last month in relation to the mean *S. mansoni* egg output. The cut-off at 100 epg stool indicates the level where the perception changed distinctively.

Potential confounding by other intestinal parasites

Besides sex, age and village, additional potential confounders of the association between questions and infection status with *S. mansoni* were analysed by logistic regression modelling. Infections with other intestinal helminths (hookworm and *A. lumbricoides*) and pathogenic protozoa (*E. histolytica/E. dispar* and *G. lamblia*) were not found to be confounders (Table 5.3).

Signs and symptoms indicating moderate and high S. mansoni infections

All perceived signs and symptoms that may indicate an infection with *S. mansoni* were added one-by-one to the basic model made up by the variables described in Table 5.3. The corresponding odds ratios were then calculated (Table 5.4). "Having had blood in the stools during the last month" was the best predictive factor for a moderate to high infection with *S. mansoni* with an odds ratio of 2.87 (95% CI: 1.56-5.31; p<0.001). In addition, the Yacouba term '*gnon*' and the Dioula term '*toto*' showed statistically significant associations with moderate to high *S. mansoni* infections with odds ratios of 2.49 (95% CI: 1.19-5.21) and 2.47 (95% CI: 1.08-5.66). The Yacouba term '*gloujeu*', showed borderline association with an odds ratio of 1.86 (95% CI: 0.99-3.47). No statistically significant associations were found for the questions "did you have diarrhoea during the last month?" and "did you have schistosomiasis during the last month?".

Table 5.3

Potential confounders of the association between the questions on signs and symptoms and the infection status by *S. mansoni*, logistic regression modelling (CI: confidence interval).

Variable / Level	Odds ratio (95% CI)
Village	
Gueupleu	1.00
Gbatongouin	0.61 (0.30-1.21)
Mélapleu	0.53 (0.23-1.23)
Age group	
8-11 years	1.00
12 years	1.08 (0.49-2.36)
13 years	0.66 (0.29-1.51)
14-16 years	1.03 (0.44-2.39)
Sex	
Male	1.00
Female	0.95 (0.51-1.79)
Intestinal helminths	
Hookworm: positive	1.27 (0.68-2.37)
Ascaris lumbricoides: positive	0.75 (0.42-1.35)
Pathogenic protozoa	
Entamoeba histolytica/E. dispar: positive	1.63 (0.91-2.93)
G. lamblia: positive	1.06 (0.44-2.56)

Table 5.4

Best signs and symptoms to predict *Schistosoma mansoni* infections of more than 100 eggs per gram stool, as assessed by logistic regression modelling.

Signs and symptoms	Odds ratio (95% CI)	p-value
Blood in stool	2.87 (1.56-5.31)	<0.001
"*Gnon*"	2.49 (1.19-5.21)	0.014
"*Toto*"	2.47 (1.08-5.66)	0.029
"*Gloujeu*"	1.86 (0.99-3.47)	0.051
Schistosomiasis	3.61 (0.72-18.17)	0.089
Diarrhoea	1.70 (0.80-3.60)	0.165

Diagnostic performance of different signs and symptoms

The sensitivities, specificities and positive and negative predictive values for the most promising signs and symptoms are given in Table 5.5. "Having had blood in the stools during the last month" showed the highest sensitivity (47%; 95% CI: 37-57%) and negative predictive value (60%; 95% CI: 51-68%). '*Gnon*' and '*toto*', the other two signs that were significantly associated with moderate to heavy *S. mansoni* infections, resulted in higher specificities and slightly higher positive predictive values than 'blood in stool'. '*Gloujeu*' with borderline association showed the second highest sensitivity (39%; 95% CI: 30-49%). 'Schistosomiasis' showed the best specificity (98%; 95% CI: 93-100%) but a very poor sensitivity (9%; 95% CI: 4-16%).

Table 5.5
Diagnostic performance of different signs and symptoms indicating *Schistosoma mansoni* infections of more than 100 eggs per gram before praziquantel treatment.

Signs and symptoms	Sensitivity	Specificity	PV+	PV-
Blood in stool	47% (37-57%)	76% (67-84%)	66% (54-76%)	60% (51-68%)
"*Gnon*"	30% (22-40%)	86% (77-92%)	67% (52-80%)	56% (48-64%)
"*Toto*"	23% (16-33%)	90% (82-95%)	69% (51-83%)	55% (47-62%)
"*Gloujeu*"	39% (30-49%)	75% (65-82%)	60% (47-71%)	56% (47-64%)
Schistosomiasis	9% (4-16%)	98% (93-100%)	82% (48-97%)	56% (45-60%)
Diarrhoea	25% (17-35%)	85% (76-91%)	62% (46-76%)	54% (46-62%)

Changes after praziquantel treatment

Comparison of questionnaire results before and after praziquantel treatment was done for all the children who showed moderate or heavy infection before treatment (more than 100 eggs per gram stool; n=96). McNemar's chi-squared test revealed a statistically significant reduction for 'blood in stool' ($\chi^2 = 7.76$, $p < 0.01$) and the local Yacouba term '*gloujeu*' ($\chi^2 = 12.90$, $p < 0.001$). The two terms '*gnon*' and '*toto*', that were both significantly more often reported by moderately and heavily infected children before praziquantel treatment, were not significantly less reported after treatment.

5.5 Discussion

It is widely acknowledged that there is considerable day-to-day fluctuation in egg output in *S. mansoni* infection (Engels *et al.* 1996) and that analysing stool specimens from a single day would result in considerable underestimation of the true infection prevalence, especially in low endemicity areas (De Vlas & Gryseels 1992, De Vlas *et al.* 1993). In the present study, stool specimens were collected over 5 consecutive days, and the cumulative results of *S. mansoni* egg counts confirmed the underestimation of any single day result. However, it was observed, that the cumulative prevalence after 3 consecutive days (90.0%) was only slightly lower than after 4 days (92.3%) or after 5 days (92.7%, data not presented). As there was a considerable number of children that missed at least one stool sample during the 5 consecutive days, it was decided to include all children with at least 4 stool examinations for the final analysis. Consequently, the arithmetic mean egg for output from the 4 examinations was considered as the 'gold standard'. Based on the experience made, it needs to be emphasised that it is operationally difficult and costly to carry out multiple stool collections, which was also observed elsewhere (Engels *et al.* 1996). Furthermore, each additional consecutive day is likely to reduce the overall sample size because of children's lack of compliance and the increased possibility that they may be absent on a particular day. In the present study, the level of drop-outs was low and it was possible to obtain at least four stool samples from 87% of the schoolchildren.

Our work confirmed that it is feasible to carry out schistosomiasis studies in a school environment with the active participation and collaboration of school directors and teachers. Similar observations have been made elsewhere (Red Urine Study Group 1995; N'Goran *et al.* 1998). Recently, it was shown how school teachers could play an important role in schistosomiasis control programmes (Magnussen *et al.* 1997).

To assess the importance of vector-borne diseases (Kroeger & Arana 1997) and schistosomiasis in particular (Tanner *et al.* 1986, Tanner 1989, WHO 1993), it has been proposed to apply multidisciplinary approaches. In the present study, two social scientists, with a background in medical anthropology, were part of the research team. It was their responsibility to conduct the focus group discussions in order to assess schoolchildren's disease perception. It was found that terms like 'diarrhoea' and 'blood in stool' were often reported to occur in the present study area. However, there were also some common terms in the local Yacouba/Dioula languages. These findings were used to set up a schoolchildren's questionnaire which allowed the comparison of the parasitological data with the children's disease perception.

As the Kato-Katz thick smears were analysed quantitatively, this allowed disease perception to be compared with infection status. Before, Sukwa *et al.* (1986) also looked at the relationship between morbidity and intensity of *S. mansoni* infection. In the present study, an arithmetic mean egg output of 100 *S. mansoni* epg represented a distinct cut-off for 'blood in stool', '*gnon*' and '*toto*', the three signs and symptoms that showed statistically significant

associations with *S. mansoni* infections. It is well acknowledged that such cut-offs may vary from one endemic area to another (Guyatt *et al.* 1995). However, our data further support the setting of the cut-off between light and moderate infections at 100 epg, as children's perception clearly changed at this level. Interestingly, this cut-off is in full agreement with the one proposed by WHO (1993).

Previous studies undertaken in Zambia (Sukwa *et al.* 1985, Sukwa *et al.* 1986) and Brazil (Lima e Costa *et al.* 1991) found good correlations between *S. mansoni* infections and the answer 'blood in the stools'. However, it was stated that when other intestinal helminths were also endemic, those may be confounding factors. In the present study, the presence of other intestinal helminths as well as pathogenic protozoa was also assessed. Infections with hookworms and *A. lumbricoides* were frequently observed, however with only light infections (which in the case of hookworms could partly due to the unsuitable diagnostic method). *E. histolytica/E. dispar* was three times more prevalent then *G. lamblia*. However, logistic regression modelling revealed that non of these intestinal parasites confounded the association between the questions and *S. mansoni* infections. This indicated that infections with the other parasites were equally distributed between those children responding "yes" to the questions and those responding "no". An additional publication presenting the associations between the questions and infections with other intestinal parasites is in preparation.

Signs and symptoms that had a significant association with moderate to high infections were assessed for their diagnostic performance. "Having had blood in the stools during the last month" showed the highest sensitivity, and this was considerably higher than had been found elsewhere (Sukwa *et al.* 1986, Gryseels & Poldermann 1987, Proietti & Antunes 1989, Lima e Costa *et al.* 1991). No correlation was found between *S. mansoni* infection and the presence of diarrhoea, which is in agreement with Lima e Costa *et al.* (1991) but in disagreement with Sukwa *et al.* (1986). However, for *E. histolytica/E. dispar* it was found that infected children reported significantly more often to have had diarrhoea during the last month.

After the praziquantel treatment against schistosomiasis, the children's perception changed. The positivity rate of questionnaire responses of the group of children that previously had an infection of more than 100 epg dropped. For the two signs 'blood in stool' and '*gloujeu*', the drops were statistically significant.

In view of our findings, and taking into account preliminary results from an earlier study in Ethiopia (Hailu *et al.* 1995) and recent work in Tanzania (M. Booth & C. Mayombana personal communication) it is concluded that 'blood in the stool' is the most valuable sign to indicate a *S. mansoni* infection of more than 100 epg. This sign showed a moderate sensitivity (and hence a moderate negative predictive value) and a higher specificity. Other valuable signs and symptoms, as expressed in the local Yacouba/Dioula languages were '*gnon*' and '*toto*', although their sensitivities (and hence negative predictive values) were lower. Despite these moderate sensitivities the results are encouraging enough to aim for a larger scale study to test the rapid and low-cost identification of high risk communities for intestinal schistosomiasis,

using a questionnaire-based approach like that which has proved to be very successful for *S. haematobium* screening (Lengeler *et al.* 1991, Lengeler *et al.* 1992, Red Urine Study Group 1995, N'Goran *et al.* 1998).

5.6   Acknowledgements

5.7   References

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6   Rapid screening for *Schistosoma mansoni* in western Côte d'Ivoire using a simple school questionnaire

J. Utzinger [1,2,*],   E.K. N'Goran [2,3],   Y.A. Ossey [4],   M. Booth [1],   M. Traoré [2], K.L. Lohourignon [3], A. Allangba [4], L.A. Ahiba [4], M. Tanner [1] & C. Lengeler [1]

1   Swiss Tropical Institute, Department of Public Health and Epidemiology, P.O. Box, CH–4002 Basel, Switzerland

2   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

4   Grandes Endémies de Man, BP 470, Man, Côte d'Ivoire

*   Corresponding author
       Tel   ++41 61 284 8110
       Fax   ++41 61 271 7951
       e-mail   juerg.utzinger@unibas.ch

6.1 Abstract

The distribution of schistosomiasis is focal, so if the resources available for control are to be used most effectively, they need to be directed towards the individuals and/or communities at highest risk of morbidity. Rapid and inexpensive ways of doing this are needed, such as simple school questionnaires. In an *S. mansoni* endemic area in western Côte d'Ivoire correctly completed questionnaires were returned from 121 out of 134 schools (90.3%) with 12227 children interviewed individually. Parasitological validation was conducted in 60 randomly selected schools, and 5047 schoolchildren provided two consecutive stool samples for Kato-Katz thick smears. The cumulative infection prevalence of *S. mansoni* was 54.4%. Individuals infected with *S. mansoni* reported 'bloody diarrhoea', 'blood in stool' and 'schistosomiasis' significantly more often than uninfected children. At school level, Spearman rank correlation analysis showed that the cumulative school infection prevalence of *S. mansoni* was significantly correlated with the prevalence of reported bloody diarrhoea (p=0.002), reported blood in stool (p=0.014) and reported schistosomiasis (p=0.011). Reported bloody diarrhoea and reported blood in stool had the best diagnostic performance (sensitivity: 88.2%, specificity: 57.7%, positive predictive value: 73.2%, negative predictive value: 78.9%). Our work which is probably the largest of its kind ever undertaken in Africa revealed a moderate diagnostic performance of questionnaires to identify high risk individuals and/or communities of *S. mansoni*.

Key words: Côte d'Ivoire – diagnostic techniques and procedures – epidemiological studies – questionnaires – *Schistosoma mansoni* – diagnosis – schools

6.2 Introduction

Intestinal schistosomiasis caused by *Schistosoma mansoni* is widespread throughout Africa, where it is currently endemic in 40 countries (1). Because its distribution is focal, the transmission is influenced by factors such as intermediate host snail distribution, patterns of environmental contamination with human excreta and water contact by human (1-3). Parasite aggregation in space and within communities is also an important feature (4, 5). The public health significance of schistosomiasis is often underestimated because its distribution is focal and because severe disease only follows after many years of mildly symptomatic infections (1, 6). In addition, primary health care systems in Africa have to deal with many other health problems, with resources that are scarce and that need to be allocated in the most effective way (7). This explains why schistosomiasis control is often given a low priority and why national programmes are almost non-existent. At present, the large-scale identification of *S. mansoni* requires stool examination, which is labour-intensive and generally cannot not be integrated into routine health care activities (1, 7). Therefore, there is a great need for a rapid but

accurate assessment of individuals and/or communities at highest risk of intestinal schistosomiasis, so that control activities can be better focused (8).

The use of a simple self-administered questionnaire to identify communities at highest risk for *S. haematobium* proved to be very effective in more than 10 African countries with different levels of endemicity (9-14). The success of the questionnaire approach for urinary schistosomiasis arises because *S. haematobium* is generally well recognized by a specific and sensitive symptom, the presence of blood in urine. Based on these experiences, WHO has developed guidelines for use in the control of schistosomiasis by district health managers (15). Recently, the questionnaire was also validated in Côte d'Ivoire, and consequently its use was recommended as a first step for the national community-based morbidity control programme (13).

The objective of the present study was to develop and validate a similar questionnaire for the rapid identification of individuals and/or communities at high risk from *S. mansoni* infection. It was realized that the use of simple anamnestic questions would be more problematic for *S. mansoni*, since the signs and symptoms indicating an infection generally show low sensitivities and specificities, and do not yet permit operational interventions. However, recent studies conducted in the Democratic Republic of the Congo (11, 16), Ethiopia (17), Côte d'Ivoire (18) and the United Republic of Tanzania (19) suggested that presence of blood in stools is a useful indicator and its diagnostic performance for the rapid screening of *S. mansoni* should be further investigated The benefits of a rapid appraisal method would be considerable, especially if a single questionnaire would work for both schistosome species (16).

This article describes the design and validation of an *S. mansoni* questionnaire for large-scale use. Validation was performed by carrying out parasitological examinations in a random sample of schools where the questionnaire had been filled in, to determine the prevalence and intensity of *S. mansoni* infections. Since geohelminth infections could produce similar symptoms, and hence act as confounding factors (18, 20-22), their prevalences were also assessed. Prevalence of microhaematuria, an indirect indicator of *S. haematobium* infection (23) was also estimated to assess the frequency of mixed infections.

6.3   Materials and Methods

Study area

The study was carried out in the region of Man in western Côte d'Ivoire between January and June 1998. It is a known endemic area for intestinal schistosomiasis (24-26), but precise data on infection prevalence at the village level are only sparsely available. A recent study confirmed the high endemicity with a cumulative infection prevalence of 92% derived from four repeated Kato-Katz readings in three villages (18).

The study area covers approximately 2500 km^2 with a total population estimated at 250 000 at the time of the survey. The town of Man is located in the region's centre at an altitude of 320 m. It is a rapidly growing town of approximately 120 000 inhabitants. Rice, coffee and cocoa are the most important cash crops and there is small timber industry. Villagers in the rural areas are mainly engaged in subsistence farming with dry and/or wet rice, cassava, maize, banana and yams as their main crops. The mean annual precipitation is 1,600 mm (26). There are two distinct seasons: a rainy season of 7 months lasting from April to October, with peak rains in July and August, and a shorter dry season between November and March. The hydrography is dominated by rivers flowing south-north. The Ko and Nzo are the main rivers. The geographical coordinates of the schools were collected with a hand-held GPS 45 (Garmin Corp., Lenexa, USA) and are displayed in Figure 6.1.

Development and distribution of the questionnaire

The schoolchildren's questionnaire was developed based on the original French version that was used previously in the Democratic Republic of Congo (11, 16), and a slightly modified version that was successfully used in central Côte d'Ivoire (13). The questionnaire was finalized following focus group discussions with children heavily infected with *S. mansoni* and semi-structured interviews with three medical assistants in the region's main town which emphasised in particular the symptoms of 'blood in stool' and 'bloody diarrhoea' (18). Finally, last modifications were made after pre-testing in two schools. The questionnaire consisted of a list of 12 different symptoms in French and 4 in the local Yacouba and Dioula languages and a list of 9 different diseases (all in French). During preliminary testing it was found that the children attending standards 1-3 had difficulties in responding to some of the questions, and it was decided to include only children attending standards 4-6 for large scale use. The questionnaire can be obtained from the authors.

The questionnaire was accompanied by two separate forms: (i) the instructions for teachers and (ii) a blank class list. The teachers were asked to first read the instructions, then to fill in the names (in alphabetical order), sex and age of their pupils in the class list. After this, children were interviewed individually, in alphabetical order. The interview was conducted in an empty class room and answers were recorded as: "yes", "no" and "don't know". This procedure allowed us to analyse the data on both individual and school level, since individual answers could be related to individual parasitological results. The questionnaires were deposited at two regional education offices (Man 1 & 2) by the end of January 1998, and they were distributed by the existing administrative channels to all 134 primary schools.
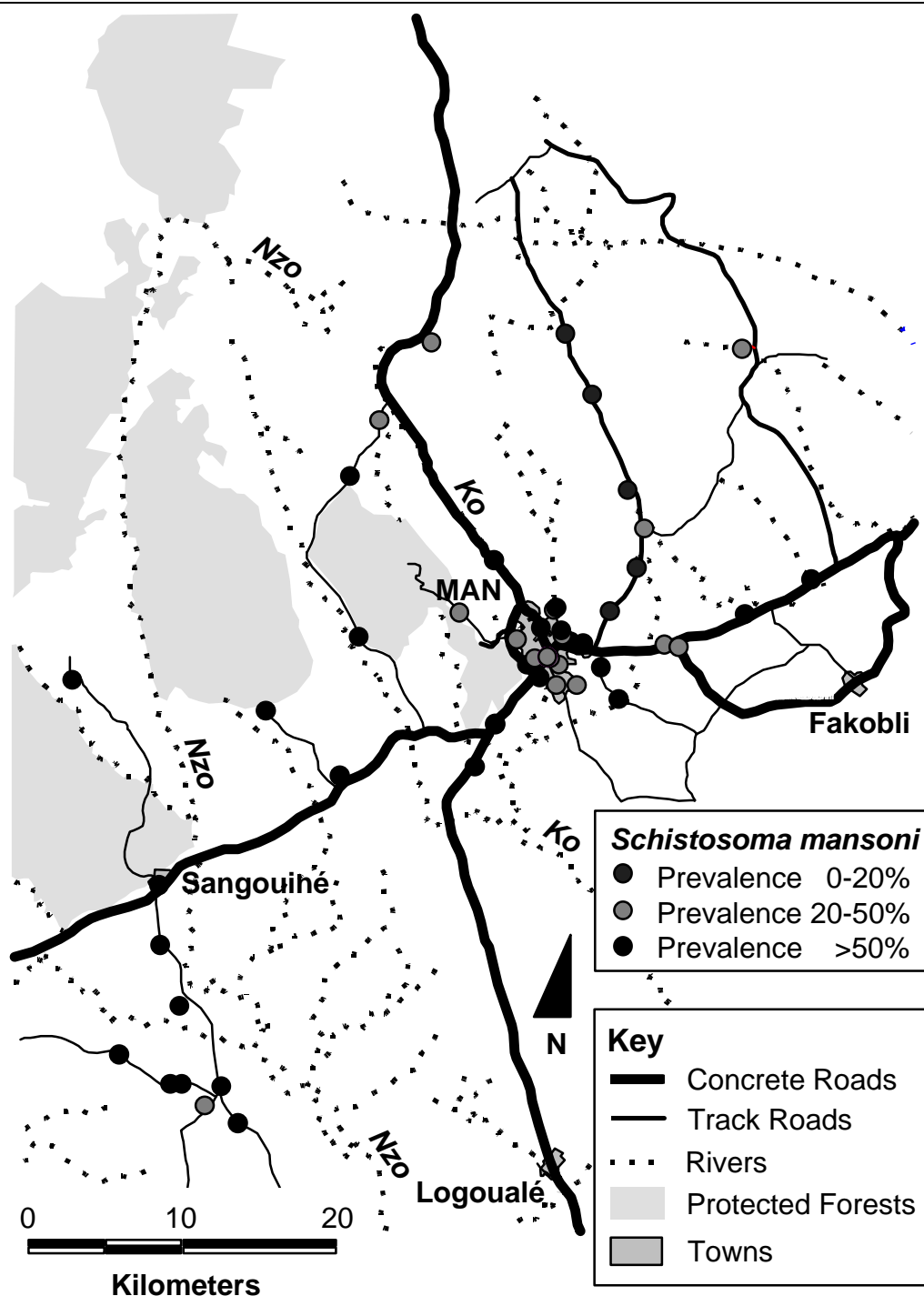
Figure 6.1

Map of the study area with the town of Man in the centre and the 60 schools were children were screened for *Schistosoma mansoni*. Prevalence of *S. mansoni* infection is shown by category: 0-20%, 20-50% and >50%.

Parasitological investigations and treatment of infected children

For parasitological validation, a simple random sample of 60 schools was drawn among the schools returning the questionnaires. The school directors were informed one day in advance that their school was one among 60 randomly selected schools where parasitological validation of questionnaire results was to be performed. The objective of the study was explained, and it was assured that all children with intestinal parasites would benefit from free treatment. After obtaining the teacher's consent, children were issued with a plastic stool container and asked to return the containers with a small portion of their own morning stool on the day of the first survey.

A laboratory team consisting of 7 people undertook field testing in 2-4 schools per day. Children's stool specimens were collected individually. At the time of stool collection children were issued with another plastic container for a second stool sample on the following day. On the spot, a single 42 mg Kato-Katz thick smear was processed according to Katz et al. ([27]). The slides were brought to the central laboratory in Man and in the afternoon, they were analysed under light microscope at low magnification by one of five experienced technicians. The total number of eggs of *S. mansoni*, hookworms, *Ascaris lumbricoides* and *Trichuris trichiura* was counted. Quality control was carried out by the senior technician on 5-10% of the slides chosen at random.

On survey day and always between 10:00 and 12:00 hours, children were provided with another small plastic container for immediate urine collection. Reagent stick testing for microhaematuria was performed with Sangur sticks (Boehringer Mannheim, Germany). The sticks were briefly dipped into the fresh stirred urine sample and after 60 seconds the colour change was read according to the manufacturer's instructions. The results were recorded as negative, 1+, 2+ or 3+.

All children who had at least one *S. mansoni* egg in any of the two Kato-Katz thick smears or a reagent stick testing result of ≥ 1+ were treated with a single oral dose of praziquantel at the recommended standard dose of 40 mg per kg body weight ([1]). Infections with hookworms, *A. lumbricoides* and/or *T. trichiura* were treated with a single oral dose of albendazole (400 mg).

Data analysis

All data derived from the questionnaires and the parasitological surveys were double entered and validated using the EpiInfo software package (version 6.04, USD Inc. Stone Mountain, USA). Daily infection prevalences of schistosomes and geohelminths were assessed in all the 60 schools. The cumulative infection prevalence was calculated for those children who provided two consecutive stool samples, using their arithmetic mean. This was considered as 'gold standard' and was used for assessing the diagnostic performance of the questionnaire.

At the individual level, a logistic regression analysis was performed for those children who had two consecutive Kato-Katz readings, a reagent stick result on day 1 and complete questionnaire results, in order to assess the most reliable reported symptom(s) and/or disease(s) predicting an infection with *S. mansoni*. At school level, Spearman rank correlation was computed between the cumulative school infection prevalence of *S. mansoni* and the questionnaire positivity rates in each school. The diagnostic performance of the questionnaire to identify a school where the children are at high risk for *S. mansoni* infection was calculated by computing the sensitivity, specificity and predictive values, including 95% confidence intervals (CI).

6.4   Results

Operational results

Within 5 weeks, correctly completed questionnaires were returned from 121 out of 134 schools (90.3%) and a total of 12227 children were interviewed individually. The median age of these children was 12 years with a range between 6 and 17 years. There were significantly more boys (7489) than girls (4738) (χ^2, 1 degree of freedom (d.f.) = 313.2, p < 0.0001), resulting in a sex ratio of 1.58. The sex imbalance tended to increase with age.

For parasitological validation, a simple random sample of 60 schools was drawn from those schools that had all classes of standards 4-6 (n = 110 schools). In total, 6,543 children were interviewed in this sub-sample. The median age was 12 years (range 7-17), with a sex ratio of 1.57 and an average of 109 children were interviewed per school.

Schistosomes and geohelminths

Overall, 5047 children (77.1% of children interviewed) provided two consecutive stool specimens for Kato-Katz thick smears. *S. mansoni* was the most common intestinal parasite, with a cumulative infection prevalence of 54.4%. Hookworm infections were underestimated in our study, as the Kato-Katz method with a clearing time of several hours is not suitable for this parasite, since eggs are rapidly digested on the slides. Despite this underestimation, hookworms were the second most prevalent intestinal parasite with an overall cumulative infection prevalence of 9.5%. Infections with *A. lumbricoides* and *T. trichiura*, showed low cumulative infection prevalences of 5.5% and 4.1%, respectively (Table 6.1).

Table 6.1

Overall cumulative results of *S. mansoni* and geohelminth infections derived from two consecutive Kato-Katz thick smears and cumulative prevalence of microhaematuria (an indirect indicator for *S. haematobium*) in 60 schools in the region of Man in western Côte d'Ivoire.

	# positive	infection prevalence (%)	95% CI (%)
Kato 1 & Kato 2 (n = 5047 children)			
S. mansoni	2747	54.4	53.0 - 55.8
Hookworm	480	9.5	8.7 - 10.4
A. lumbricoides	276	5.5	4.9 - 6.1
T. trichiura	205	4.1	3.5 - 4.6
Reagent stick day 1 (n = 5967 children)	328	5.5	4.9 - 6.1

S. mansoni infections were divided into four categories: (i) no infection; (ii) light infection: 1-100 eggs per gram (epg) of stool; (iii) moderate infection: 101-400 epg and (iv) heavy infection: > 400 epg. The results derived from the first and the second Kato-Katz readings, as well as the cumulative results, are presented in Table 6.2. Daily infection prevalences were 45.0% and 45.8% and the prevalence of daily intensities of >100 epg was 28.1% and 28.5%. The cumulative prevalence of this intensity level was 31.0%. There was a large range in infection prevalence measured among the 60 schools, ranging from 4.0% to 94.0%. There was also a large range in the prevalence of infections above 100 epg with a minimum of 1.6% and a maximum of 79.5%.

Table 6.2

Point and cumulative infection status of *S. mansoni*, as assessed by two consecutive Kato-Katz thick smears (epg = eggs per gram of stool).

	Prevalence (%)		
	Kato 1 (n = 5811)	Kato 2 (n = 5493)	Kato 1& 2 (n = 5047)
All infections	45.0	45.8	54.4
All infections > 100 epg	28.1	28.5	31.0
Children's infection status (epg)			
Negative (0)	55.0	54.2	45.6
Light infection (1-100)	16.9	17.3	23.4
Moderate infection (101-400)	14.7	15.3	16.9
Heavy infection (> 400)	13.4	13.2	14.1

Boys (59.4%) were significantly more often infected with *S. mansoni* than girls (46.7%, χ^2, 1 d.f. = 76.2, p < 0.0001). Amongst infected children the median infection intensity of boys (156 epg) was significantly higher than that of girls (108 epg, χ^2, 1 d.f. = 13.4, p < 0.001).

A total of 5967 children provided a urine sample on day 1 and in 328 cases (5.5%) the reagent stick result was positive. Since reagent stick testing has a specificity well below 100% most of these are likely to be false positives. Initially, it was planned to screen all children for microhaematuria on two consecutive days. However, after screening in 40 schools and obtaining such a low point prevalence it was obvious that *S. haematobium* was very rare in the area and it was decided that the cost of a second reagent stick testing was not justified.

Association between questionnaire and parasitological data at the individual level

Two consecutive stool samples, a urine reagent stick testing result on day 1, as well as complete answers to the questionnaire, were obtained from 4788 children. For these children, logistic regression analysis at the individual level confirmed that an infection with *S. mansoni* was significantly associated with sex (adjusted odds ratio: 1.14, 95% CI: 1.10-1.18, p<0.001) and age (adjusted odds ratio: 0.65, 95% CI: 0.58-0.74, p<0.001). Children infected with *S. mansoni* were more likely to have a hookworm infection (adjusted odds ratio: 1.30, 95% CI: 1.06-1.60, p<0.001). No such positive associations were found for *A. lumbricoides* and *T. trichiura* (Table 6.3). It was also found that *S. mansoni* infected children were more likely to have low-level microhaematuria (adjusted odds ratio: 1.91, 95% CI: 1.45-2.53, p < 0.001).

Multivariate analysis identified reported blood in stool and reported bloody diarrhoea as those symptoms with the strongest association with an *S. mansoni* infection. The adjusted odds ratios were 1.59 (95% CI: 1.38-1.83, p < 0.001) and 1.34 (95% CI: 1.14-1.58, p < 0.001), respectively (Table 6.3). The answer "yes" to "do you have schistosomiasis?" was given significantly more often among *S. mansoni* infected children, but the adjusted odds ratio was low. There was also a significant odds ratio between reported skin disease and an infection with *S. mansoni*, but this may be a chance finding which would not be surprising given the number of variables that were investigated. No significant odds ratios were found between an *S. mansoni* infection and reported abdominal pain, reported presence of worms in the faeces and reported diarrhoea (Table 6.3).

Association between questionnaire and parasitological data at the school level

The Spearman rank correlation test revealed significant associations between the cumulative school infection prevalences of *S. mansoni* and prevalences of reported bloody diarrhoea (rho = 0.39, p = 0.002), reported blood in stool (rho = 0.32, p = 0.014) and reported schistosomiasis (rho = 0.33, p = 0.011) (Table 6.4). These relations are illustrated in Figures 6.2a-6.2c.

Table 6.3

Logistic regression modelling at individual level to assess potential confounders of the association between an infection with *S. mansoni* and other intestinal parasites and best performing reported symptoms to predict an *S. mansoni* infection (n = 4788 children).

Variable	Adjusted odds ratio (95% CI)	Likelihood ratio statistics	p-value
Children surveyed			
Sex	**1.14 (1.10-1.18)**	**49.08**	**< 0.001**
Age	**0.65 (0.58-0.74)**	**48.00**	**< 0.001**
Intestinal parasites			
Hookworm	**1.30 (1.06-1.60)**	**6.14**	**0.013**
A. lumbricoides	0.85 (0.66-1.09)	1.65	0.199
T. trichiura	0.99 (0.73-1.34)	0.00	0.952
Reported symptoms			
Blood in stool	**1.59 (1.38-1.83)**	**41.90**	**< 0.001**
Bloody diarrhoea	**1.34 (1.14-1.58)**	**12.66**	**< 0.001**
Schistosomiasis	**1.32 (1.04-1.66)**	**5.43**	**0.020**
Skin disease	**1.18 (1.01-1.37)**	**4.26**	**0.039**
Worm in feaces	1.12 (0.98-1.27)	2.89	0.089
Abdominal pain	1.03 (0.91-1.17)	0.25	0.619
Diarrhoea	1.02 (0.89-1.16)	0.06	0.800

During preliminary analysis of the data, it became evident that some schools had very high male:female sex ratios. Since infections occurred more often amongst boys, we additionally investigated whether extreme sex ratios could affect the relationship between infection prevalence and reported symptoms. We gradually removed schools from the dataset, starting with schools with the highest sex ratios, and repeated the analysis at each step. This process revealed that schools with a lower sex ratio had a higher degree of correlation between the prevalences of *S. mansoni* infections and prevalences of reported blood in stool. For example, schools with a sex ratio of 2 or less had a Spearman rank correlation coefficient of 0.48 (n=41, p=0.002), and schools with a sex ratio ≤ 1.6 had a Spearman rank correlation coefficient of 0.56 (n=27, p=0.002). The improvement in the relationship is shown in Fig 6.2d, which displays data from schools with a sex ratio ≤ 1.6. Interestingly, when sex-stratified analysis was conducted, the correlations were not improved. This points towards the fact that it was not the gender per se that led to weak correlations, but rather that schools with a high sex-ratio were special in some way.
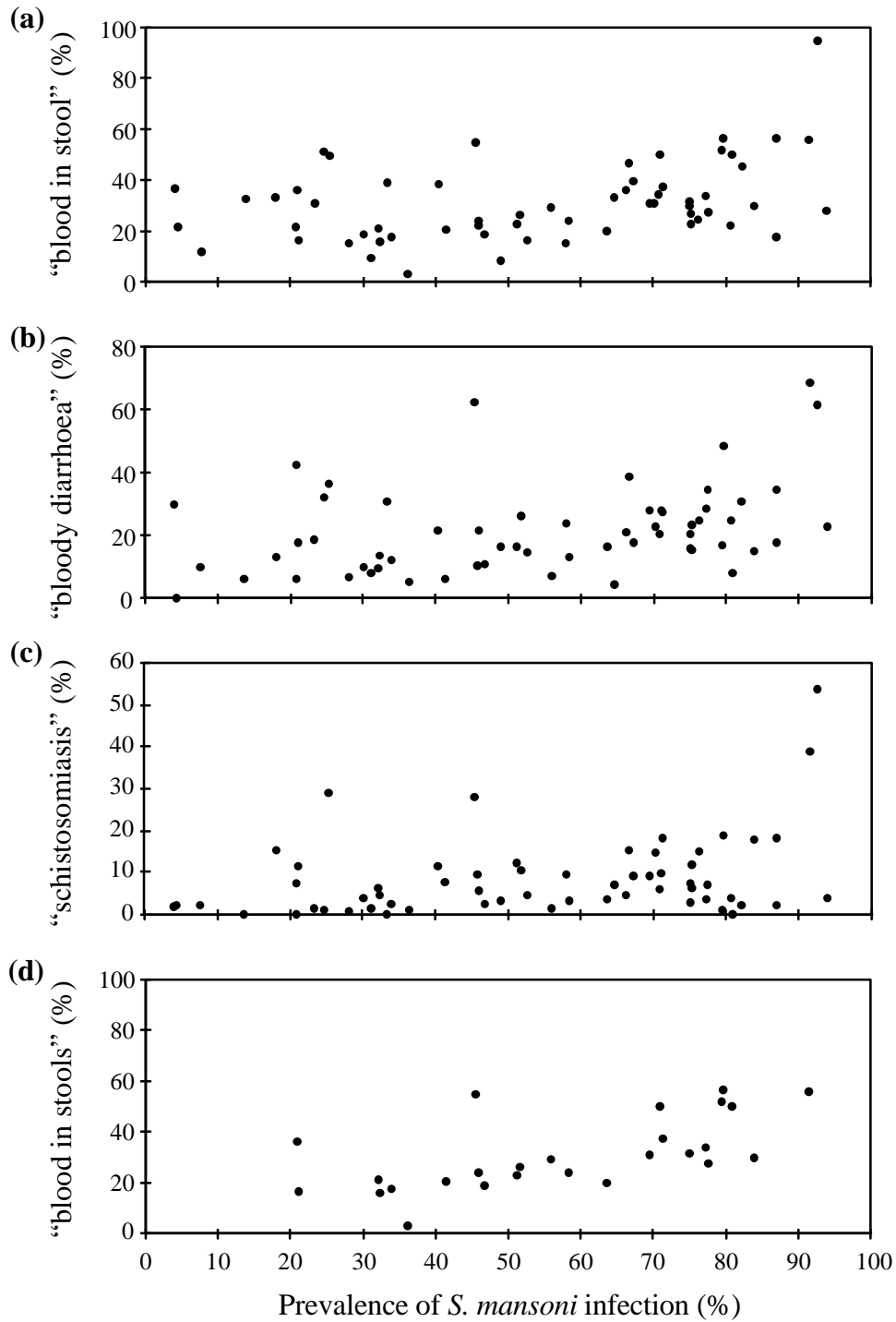
Figure 6.2
Relationship between the cumulative school infection prevalence of *S. mansoni* and the prevalence of reported symptoms: (a) reported blood in stool (all schools, n=60); (b) reported bloody diarrhoea (all schools, n=60); (c) reported schistosomiasis (all schools, n=60); (d) reported blood in stool (only those school with a sex-ratio ≤ 1.6, n=27).

Spearman rank correlation analysis was also performed with different levels of *S. mansoni* infection intensities. Interestingly, *S. mansoni* infection prevalence was better correlated with reported blood in stool, bloody diarrhoea or reported schistosomiasis than different intensity measures of infection (Table 6.4). When we repeated the analysis with the reduced data set (schools with sex ratio ≤ 1.6), there was an increase in the correlation coefficient when comparing parasitological measures and reported blood in stool or reported bloody diarrhoea at school level. In contrast, when comparing reported schistosomiasis and parasitological measures, the correlation coefficients were significantly reduced (Table 6.4).

Table 6.4

Spearman rank correlation analysis for reported blood in stool, reported diarrhoea and reported schistosomiasis for five different criterias for *S. mansoni* infection (infection prevalence and 4 different intensity levels).

	Reported blood in stool		Reported bloody diarrhoea		Reported schistosomiasis	
	rho	p-value	rho	p-value	rho	p-value
All schools (n=60)						
Infection prevalence	0.32	0.014	0.39	0.002	0.33	0.011
Infection intentsity > 100 epg	0.26	0.047	0.33	0.010	0.29	0.022
Infection intentsity > 400 epg	0.16	0.237	0.33	0.010	0.33	0.010
Arithmetic mean intensity	0.21	0.101	0.28	0.030	0.33	0.010
Geometric mean intensity	0.30	0.021	0.37	0.004	0.34	0.008
Only schools with sex-ratio ≤ 1.6 (n=27)						
Infection prevalence	0.56	0.002	0.43	0.024	0.05	0.820
Infection intentsity > 100 epg	0.62	0.001	0.39	0.042	0.06	0.764
Infection intentsity > 400 epg	0.59	0.001	0.45	0.018	0.22	0.271
Arithmetic mean intensity	0.60	0.001	0.48	0.012	0.18	0.373
Geometric mean intensity	0.62	0.001	0.45	0.018	0.09	0.641

Diagnostic performance of the questionnaire at the school level

The first step to calculate the diagnostic performance of the schoolchildren's questionnaire was to choose a detection threshold, i.e. a prevalence rate above which the school would be termed 'high risk'. According to Montresor et al. (28) we used a threshold of 50%. For this threshold, we then determined the positivity rates of reported symptoms and reported diseases that would lead to the best diagnostic performance: It was 22% for reported blood in stool, 14% for reported bloody diarrhoea and 4% for reported schistosomiasis.

The sensitivity, specificity and predictive values for reported blood in stool, reported bloody diarrhoea and reported schistosomiasis are given in Table 6.5. The two reported symptoms 'blood in stool' and 'bloody diarrhoea' showed exactly the same diagnostic performance with a sensitivity of 88.2% (95% CI: 71.6-96.2%), a specificity of 57.7% (95% CI: 37.2-76.0%), a positive predictive value of 73.2% (95% CI: 56.8-85.2) and a negative predictive value of 78.9% (95% CI: 53.9-93.0%). Reported schistosomiasis resulted in slightly lower predictive values: positive predictive value: 68.6% (95% CI: 50.6-82.6%); negative predictive value: 60.0% (95% CI: 38.9-78.2%).

Table 6.5

Diagnostic performance of reported symptoms and/or diseases indicating an infection with *S. mansoni*. Threshold to detect a high risk school set at an infection prevalence of *S. mansoni* of 50% according to Montresor et al. (1998; Ref 28). PPV: Positive predictive value; NPV: negative predictive value.

Reported symptoms and/or diseases	Questionnaire threshold (%)	Diagnostic performance in % (95% CI)			
		Sensitivity	Specificity	PPV	NPV
Blood in stool	22	88.2 (71.6-96.2)	57.7 (37.2-76.0)	73.2 (56.8-85.2)	78.9 (53.9-93.0)
Bloody diarrhoea	14	88.2 (71.6-96.2)	57.7 (37.2-76.0)	73.2 (56.8-85.2)	78.9 (53.9-93.0)
Schistosomiasis	4	70.6 (52.3-84.3)	57.7 (37.2-76.0)	68.6 (50.6-82.6)	60.0 (38.9-78.2)

6.5   Discussion

Counting eggs in stool samples is currently the most widely used approach in epidemiological studies which aim to quantify the prevalence and intensity of infection due to *S. mansoni* or geohelminths. The Kato-Katz method (27) is relatively easy to perform, requires only a minimum of equipment and is suitable in many situations for direct application in the field. Most studies analyse single thick smears, which gives reliable estimates of the 'true' infection prevalence of *S. mansoni* only in high endemicity areas (29, 30). When emphasis is placed on individual diagnosis, it is therefore recommended to collect stool specimens over several consecutive days. However, this is operationally difficult and costly, and is clearly not feasible for large scale screening (31). In the present study, schoolchildren's stool specimens were collected over two consecutive days. This procedure allowed us to detect an additional 20% of children who were egg-negative on a single occasion. Testing on additional days would have been desirable but was operationally not feasible bearing in mind the large scale of the study.

The use of questionnaires is a promising alternative to egg counting for rapid and low-cost identification of individuals and/or communities at highest risk of infection. Questionnaires have been used successfully to screen for *S. haematobium* in Africa with diagnosis at community level as the main objective (9-11, 13, 14, 32-34). There is some recent evidence from Tanzania that self-reporting of blood in urine may also be useful for individual diagnosis of *S. haematobium* (12, 19, 35).

In the case of *S. mansoni,* a number of epidemiological studies have been performed to assess clinical signs and reported symptoms that may indicate an infection. In many areas of sub-Saharan Africa, a significant association has been found between *S. mansoni* infection and the presence and/or reports of blood in the stools (18, 20, 22, 36-43). All these studies revealed low to moderate sensitivities and hence low to moderate negative predictive values. The present study was probably the largest of its kind yet undertaken to evaluate the use of questionnaires for rapid screening of *S. mansoni* with emphasis on individual and community diagnosis. The study confirmed that individuals infected with *S. mansoni* reported significantly more often 'blood in stool', however, the adjusted odds ratio was only 1.59. The sensitivity and negative predictive value of reported blood in stool were therefore modest: 37% and 51%, respectively. These values are within the range of values estimated in all the preceding work.

Previous studies have also found that an infection with *S. mansoni* is often significantly associated with the presence of diarrhoea and particularly bloody diarrhoea (20, 44, 45). As with reported blood in stool, sensitivities and hence negative predictive values are generally low to moderate. Again, our results lie within the range of values reported by other workers.

It has been suggested that low sensitivities of reported blood in stool and reported bloody diarrhoea could be partly explained by the confounding effect of other intestinal parasites (20-22). In a multivariate analysis in the same area, other intestinal parasites did not act as confounders (18). Most recently, attributable risk calculations revealed that a substantial fraction of bloody stool episodes could be attributable to an infection with *S. mansoni* (46, 47), indicating that other parasites are unlikely to affect the relationship to an extensive degree.

We also found a significant correlation between *S. mansoni* infection and reported schistosomiasis at the individual level, but the adjusted odds ratio of 1.31 was very low. Interestingly, a previous study in the Democratic Republic of Congo showed a much better correlation between an infection with *S. mansoni* and reported schistosomiasis (16). We found no significant correlation between an *S. mansoni* infection and reported diarrhoea, which is in contrast to Gryseels (45).

Analysis at the school level revealed that prevalences of reported bloody diarrhoea and reported blood in stool were both significantly correlated with the cumulative infection prevalence of *S. mansoni*. Other studies have found also a positive correlation between the prevalence of reported blood in stool and infection prevalence, based on analysis of single stool samples, in the Democratic Republic of Congo (16), Ethiopia,(17) and Tanzania (19). When all schools were included in the present analysis, the correlation coefficients were low, as

illustrated by the considerable scatter in the data. By removing schools with high sex ratios, we were able to considerably improve the correlations, indicating that schools with a bias towards males had different characteristics than the rest of the schools. We are not sure of the nature of these differences, but these results nonetheless indicate that these factors are important and need to be studied in more details.

In light of these results, it may be that the questionnaire we used was not sufficiently sophisticated, and could be improved by the addition of questions focusing on risk factors for infection. A wider range of factors was investigated in a study in Brazil, where migratory status, frequent reported water contacts, history of swimming and history of fishing correlated significantly with an *S. mansoni* infection ([48]). However, the diagnostic performance of such explanatory variables may change considerably from one community to another, and their generalisation might be difficult ([49]). A study in China considered not only multiple risk factors but also multiple symptoms, and found that a combination of six key variables resulted in sensitivities and specificities above 90% for identifying infected children ([50]). One of the key factors was previous treatment history for schistosomiasis, which might explain the good diagnostic performance, since the community had been exposed to schistosomiasis and its control for a long time and had a clear perception of the disease. However, a question about previous treatment history would have been useless in the present study, as treatment had never been carried out before the study took place. This is likely to be the case in many other African countries.

We conclude that there is still a considerable amount of research needed to finally present a rapid, low-cost and reliable screening tool for *S. mansoni* for large scale use. There seems to be firm evidence that relying on the results of anamnestic questions alone to identify individuals and/or communities at high risk of *S. mansoni* infection is insufficient. We therefore argue that a combination of reported symptoms and risk factors could increase the diagnostic performance of questionnaires. In this light, it is also important to decide whether the emphasis should be placed on individual (for clinical practice) or community (for public health) diagnosis which was recently discussed by Barreto ([51]).

6.6   Acknowledgements

6.7   References

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7 Simple anamnestic questions and recalled water contact patterns for self-diagnosis of *Schistosoma mansoni* infection among schoolchildren in western Côte d'Ivoire

Jürg Utzinger [1,2], Eliézer K. N'Goran [2,3], Marcel Tanner [1] and Christian Lengeler [1,$]

1   Swiss Tropical Institute, Department of Public Health and Epidemiology, PO Box, CH–4002 Basle, Switzerland

2   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

$ Corresponding author
      Tel: + 41 61 284 82 83
      Fax: + 41 61 271 79 51
      e-mail: christian.lengeler@unibas.ch

7.1 Abstract

A study to determine the diagnostic performance of simple anamnestic questions and recalled water contact patterns for self-diagnosis of *Schistosoma mansoni* infection was carried out in western Côte d'Ivoire. A total of 322 schoolchildren were screened over four consecutive days with the Kato-Katz technique to assess *S. mansoni* and concurrent geohelminth infections. Children were individually interviewed by teachers using a standardized questionnaire asking about symptoms, reported diseases and water contact patterns. The cumulative infection prevalence of *S. mansoni* was 76.4%. Univariate statistics revealed a significant association between the level of *S. mansoni* infection and three recalled water contact patterns: (i) fishing with nets, (ii) swimming/bathing and (iii) crossing rivers; but no significant association with reported symptoms and/or reported diseases. Multivariate analysis revealed significant adjusted odds ratios for crossing the river Tchéorbour (3.90; p = 0.007), crossing the river Sonbour (3.90; p = 0.008) and swimming/bathing in the latter (3.28; p = 0.017). The diagnostic performance of these water contact patterns was characterised by high specificities but low sensitivities, hence negative predictive values. It is concluded that in the village studied here, recalled water contact patterns were more useful variables than anamnestic questions for schoolchildren's self-diagnosis of *S. mansoni* infection, but no generalization of these findings beyond this population is possible at this time.

Key words: Côte d'Ivoire – Disease perception – Questionnaires – *Schistosoma mansoni* – Schistosomiasis – Self-diagnosis – Water contact patterns

7.2 Introduction

Questionnaires have been widely used for community diagnosis of *Schistosoma haematobium* infection in several African countries. When compared to standard parasitological diagnosis, they have proved to be reliable, rapid, non-intrusive and highly cost-effective (1-7). This success was explained by the fact that *S. haematobium* is a chronic disease that is easily recognized by a specific symptom, the presence of blood in urine. Recently, self-reporting of blood in urine was found to be useful for individual diagnosis of *S. haematobium* infection (8-10).

The extension of the questionnaire procedure to *S. mansoni* has been tested recently. Reported blood in stool and/or reported bloody diarrhoea were found to be the most useful symptoms for diagnostic purposes in surveys undertaken in Ethiopia (11), Tanzania (12) and Côte d'Ivoire (13). A positive answer to the question "do you have schistosomiasis" was the best indicator to screen for high risk communities in the Democratic Republic of Congo (4). However, in most studies, the diagnostic performance of the questionnaires was only moderate, and it was concluded that further research is needed before recommending questionnaires for large scale screening for *S. mansoni* (13, 14). Other studies focused on

individual diagnosis of *S. mansoni*, and self-reported blood in stool was found to give the best diagnostic performance, but sensitivity and specificity values were only moderate (15-18).

Another approach of risk assessment was used in Brazil, where socio-demographic variables and recalled water contact patterns were investigated in addition to perceived symptoms as predictors for an infection with *S. mansoni*. Results showed that questionnaires might be an alternative for self-diagnosis of *S. mansoni* (19-24). However, parasitological validation in most of these surveys was performed with a single or a double Kato-Katz thick smear, which probably led to many infections (especially the light ones) being missed (25). This might account to some extent for the moderate diagnostic performance.

A recent study in China assessed the diagnosis performance of questionnaires for self-diagnosis of *S. japonicum* infection. Sensitivity and specificity values above 90% were obtained to identify infected schoolchildren, using a combination of six questions: episodes of diarrhoea, frequency of water contact, school grade attained, weakness, past history of *S. japonicum* infection(s), and whether a subject had been previously treated for schistosomiasis (26).

The experience gained in Brazil and China indicated that a combination of simple anamnestic questions and recalled water contact patterns might be useful for self-diagnosis of *S. mansoni* infection. The attempt of the present study, which is the first of its kind yet undertaken in Africa, was to determine the most important explanatory variables for self-diagnosis of *S. mansoni* infection and to assess the diagnostic performance of these variables.

7.3   Materials and Methods

Study area and population

The study was carried out between November and December 1998 in Fagnampleu, a village in western Côte d'Ivoire which is located 20 km east of Man, the district's main town. There are two distinct seasons, with rains occurring between April and September and a mean annual precipitation of 1,600 mm (27). There are two permanent rivers flowing through the village: the Sonbour and the Tchéorbour. According to the community health worker, malaria and intestinal schistosomiasis are both endemic. The latter is confirmed by referring patients with persistent abdominal pain and/or bloody stools to the laboratory in the town of Man for microscopical stool examination. In a recent survey in this village, 86% of the schoolchildren attending standards 4-6 were found to have eggs of *S. mansoni* (13). The study objectives were explained in detail with the chief and authorities of the village, and the school director, who all gave their consent. All 354 children registered in the school year of 1998/99 participated in the study.

Parasitological survey for Schistosoma mansoni and geohelminths

The teachers prepared class lists with the name, age and sex of the schoolchildren. The day before the first survey, children were issued with transparent plastic containers (volume 125 ml), and asked to return the containers the following day with a small portion of their morning stools. This procedure was repeated over four consecutive days.

The stool specimens were brought to the laboratory in Man and procedures were designed to examine *S. mansoni* and concurrent geohelminth infections. A single 42 mg Kato-Katz thick smear was prepared from each specimen according to Katz *et al.* (28). After the slides were allowed to clear for 45 min they were examined within 1 hour under a light microscope (Wild Heerbrugg, Switzerland) at 100x magnification by one of five experienced microscopists. The total number of eggs of *S. mansoni*, hookworms, *Trichuris trichiura* and *Ascaris lumbricoides* counted. For quality control, the senior microscopist re-examined 10% of the slides, randomly selected.

Questionnaire survey and treatment

A questionnaire was prepared asking about 5 symptoms (blood in stool, bloody diarrhoea, abdominal pain, headache and fever), 5 diseases (diarrhoea, schistosomiasis, intestinal worms, malaria, skin disease) and six water contact patterns. The symptoms and diseases were chosen on the basis of focus group discussions carried out in a preceding study in the same area (18, 29). Based on interviews with the community health worker, the school director and infected schoolchildren, the predominant water contact patterns were identified: crossing rivers, swimming/bathing, fishing with nets, fishing with hooks-and-lines, washing cloths and water use for gardening. The first three questions on water contact patterns were first asked generally (e.g. "did you cross rivers during the last month?"), and then more specifically (e.g. "did you cross the river Sonbour during the last month?"). The teachers interviewed the schoolchildren individually. All questions were asked in French, the official school language in Côte d'Ivoire, and answers were recorded as "yes", "no" or "don't know".

The day after the questionnaires survey, all children received a treatment of praziquantel in two doses of 30 mg/kg a few hours apart.

Data management and statistical analysis

All data were double-entered and verified using EpiInfo software (version 6.04; Centres for Disease Control and Prevention, Atlanta, Georgia, USA). For final analysis, only those children with four consecutive Kato-Katz thick smears and who completed the questionnaire were included. Day-to-day variation and cumulative results of *S. mansoni* egg-output were calculated. The arithmetic mean of egg output from the four readings was used to classify the level of *S. mansoni* infection into four groups: (i) no infection; (ii) light infection: 1-100 eggs per gram (epg); (iii) moderate infection: 101-400 epg and (iv) heavy infection: > 400 epg.

Univariate statistics were used to assess the effect of sex and age on infection level, with age classified into three groups: (i) 6-8 years, (ii) 9-11 years and (iii) 12-14 years. Chi-square (χ^2) test for trend was used to assess whether any reported symptoms and/or diseases and/or recalled water contact patterns showed significant correlations with the level of *S. mansoni* infection.

Multivariate analysis using logistic regression was performed to assess whether age, sex, the presence of geohelminths, reported symptoms and/or diseases, and/or recalled water contact patterns were related to an infection with *S. mansoni*. A first model was established, defining *S. mansoni* infected children as cases, and incorporating all variables. Then, the non-significant associations were removed with a backward and step-wise elimination technique. For those associations that remained significant, their adjusted odds ratio (including 95% confidence intervals), the likelihood ratio and the p-values were calculated. The same procedure was also used in a second model that defined cases as children with an *S. mansoni* infection of more than 100 epg.

Sensitivity, specificity and predictive values were calculated to assess the diagnostic performance of the most reliable variables predicting any (> 0 epg) or a moderate to heavy (> 100 epg) infection with *S. mansoni*. Finally, it was analysed whether any combination of children's answers of reported symptoms and/or reported diseases and/or reported water contact patterns improved the diagnostic performance for self-diagnosis of *S. mansoni*.

7.4   Results

Operational results

Of the 354 children registered in the school, four consecutive Kato-Katz thick smears and complete questionnaire results were obtained from 322 children (91.0%). Their mean age was 9.4 ± 2.1 years (range $6 - 14$ years). The mean age of boys (9.6 ± 2.2 years) was slightly higher than that of girls (9.0 ± 2.0 years; Kruskal-Wallis H = 7.19, p = 0.007). There were significantly more boys (190) than girls (132; χ^2, 1 degree of freedom (d.f.) = 5.27; p = 0.022).

Infections with Schistosoma mansoni and geohelminths

Daily infection prevalence of *S. mansoni* ranged between 55.6% and 58.1% and after four days reached a cumulative infection prevalence of 76.4%. Daily prevalences of infections above 100 epg ranged between 33.5% and 35.5%, and the cumulative prevalence was 41.0%. The cumulative infection prevalence of heavy infections (> 400 epg) was 16.5% (Table 7.1).

Table 7.1

Day-to-day variation and cumulative results of *S. mansoni* egg output estimated in single 42 mg Kato-Katz thick smears (n = 322 children; epg = egg per gram stool).

	S. mansoni infection prevalence (%)				
	Day 1	Day 2	Day 3	Day 4	Cumulative
All infections (%)	58.7	57.1	58.1	55.6	76.4
All infections > 100 epg (%)	33.5	34.8	35.4	34.2	41.0
All infections > 400 epg (%)	14.3	16.5	14.3	14.0	16.5

Hookworm eggs were also observed frequently with a cumulative prevalence of 59.9%. The prevalence of hookworm is, however, likely to have been under-estimated, since the Kato-Katz technique with a clearing time varying between 45 to 135 minutes is not ideal for hookworm detection. Infections with *T. trichiura* and *A. lumbricoides* were only found in 11 (3.4%) and 7 children (2.2%), respectively.

Univariate analysis

Univariate statistics revealed that there was no significant association between the level of *S. mansoni* infection and sex (χ^2, 3 d.f. = 0.90, p = 0.825) but a highly significant association with age, as older children were more often infected (χ^2, 6 d.f. = 29.71, p < 0.001).

It was interesting to note that reported blood in stool was not significantly associated with the level of *S. mansoni* infection (χ^2 for trend = 2.04, p = 0.154) and, non-infected children reported blood in stool more often than lightly infected children (Table 7.2). Of the other symptoms, only reported headache showed a significant association with the level of *S. mansoni* infection (χ^2 for trend = 5.76, p = 0.016) but this might be a chance finding. Reported 'schistosomiasis' was not significantly associated with the level of *S. mansoni* infection (χ^2 for trend = 2.09, p=0.149).

There were three recalled water contact patterns that showed clear associations with the level of *S. mansoni* infection intensities: crossing rivers (χ^2 for trend = 12.53, p < 0.001; Figure 7.1a), fishing with nets (χ^2 for trend = 9.41, p = 0.002; Figure 7.1b) and swimming/bathing (χ^2 for trend = 9.54, p = 0.002; Figure 7.1c). These significant relationships were observed for both rivers, but for the river Sonbour it was found to be consistently stronger than for the river Tchéorbour (Table 7.2).
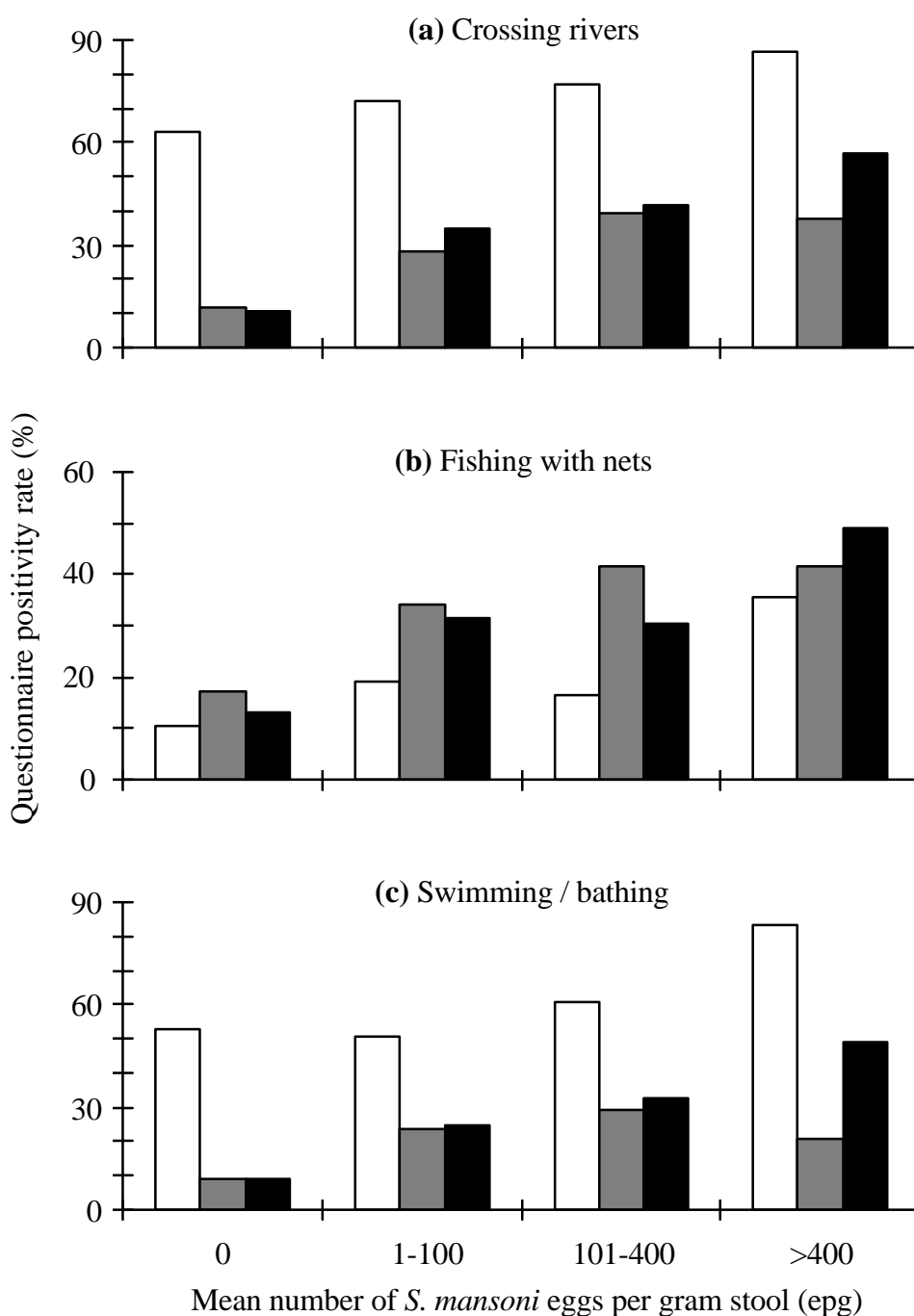
Figure 7.1

Percentage of children responding 'yes' to the question crossing rivers (a), fishing with nets (b) and swimming/bathing in rivers (c) in relation to the mean *S. mansoni* egg output White bars: general question, grey bars: specific quesiton for river Sonbour, black bars: specific question for river Tchéorbour.

Table 7.2

Percentage of children responding "yes" to different questions asked by their head teachers in relation to the level of *S. mansoni* infections. Chi square (χ^2) for trend statistics.

Question	Level of *S. mansoni* infection intensity in epg (%)				χ^2 for trend	p-value
	0	1-100	101-400	>400		
Reported symptoms						
Headache	51.3	65.8	70.9	69.8	5.76	0.016
Bloody diarrhoea	46.1	42.1	29.1	34.0	4.12	0.042
Blood in stool	48.7	34.2	49.4	56.6	2.04	0.154
Water contact patterns						
Crossing rivers	52.6	50.9	60.8	83.0	12.53	<0.001
Crossing river Sonbour	9.2	24.6	32.9	49.1	26.44	<0.001
Crossing river Tchéorbour	9.2	23.7	29.1	20.8	4.07	0.044
Fishing with nets	10.5	19.3	16.5	35.8	9.41	0.002
Fishing with nets Sonbour	13.2	31.6	30.4	49.1	16.20	<0.001
Fishing with nets Tchéorbour	17.1	34.2	41.8	41.5	10.50	0.001
Swimming/bathing	63.2	71.9	77.2	86.8	9.54	0.002
Swimming/bathing Sonbour	10.5	35.1	41.8	56.6	30.07	<0.001
Swimming/bathing Tchéorbour	11.8	28.1	39.2	37.7	14.09	<0.001

Multivariate analysis

In the first logistic model, cases were defined as those children who had a least one positive stool examination for *S. mansoni* eggs. Multivariate analysis revealed that sex, age, reported symptoms and reported diseases showed no significant odds ratios (Table 7.3). In contrast, crossing the river Tchéorbour (adjusted odds ratio 3.90, 95% confidence interval (CI): 1.38-11.00, p = 0.007), crossing the river Sonbour (adjusted odds ratio 3.90, 95% CI: 1.37-11.11, p = 0.008) and swimming/bathing in the river Sonbour (adjusted odds ratio 3.28, 95% CI: 1.19-9.07, p = 0.017) all showed significant odds ratios. Swimming/bathing in the river Tchéorbour showed no significant odds ratio, nor did any of the other recalled water contact patterns. Interestingly, the general questions "did you cross rivers during the last month?" or "did you swim/bathe during the last month?" showed no significant associations with an *S. mansoni* infection, whereas probing for the location, e.g. "did you cross the river Tchéorbour?", resulted in a significant odds ratio (Table 7.3).

Table 7.3

Multivariate analysis to determine the most reliable questions predicting an infection with *S. mansoni* (logistic regression modelling; n = 322 children; CI: confidence interval).

Variable	Adjusted odds ratio (95% CI)	Likelihood ratio statistics	p-value
Children surveyed			
Sex	1.33 (0.74-2.40)	0.90	0.342
Age group	1.21 (0.74-1.98)	0.59	0.441
Reported symptom			
blood in stool	0.66 (0.36-1.21)	1.80	0.180
bloody diarrhoea	1.08 (0.58-2.02)	0.06	0.810
Recalled water contact pattern			
Crossing rivers	0.54 (0.28-1.05)	3.34	0.068
Crossing river Sonbour	**3.90 (1.37-11.11)**	**7.11**	**0.008**
Crossing river Tchéorbour	**3.90 (1.38-11.00)**	**7.26**	**0.007**
Swimming/bathing	1.31 (0.63-2.73)	0.53	0.468
Swimming/bathing Sonbour	**3.28 (1.19-9.07)**	**5.71**	**0.017**
Swimming/bathing Tchéorbour	2.00 (0.77-5.16)	2.13	0.144

In the second model, all children with a mean egg-output of more than 100 epg (moderate or heavy infections) were defined as cases. Multivariate analysis revealed a significant association with age (adjusted odds ratio 1.61, 95% CI: 1.09-2.38, p = 0.016) but no significant association with sex (Table 7.4). The symptom 'blood in stool' was significantly more often reported by those children with more than 100 epg when compared with the uninfected or lightly infected children (adjusted odds ratio 1.73, 95% CI: 1.03-2.91, p = 0.037). Reported bloody diarrhoea showed borderline significance, however, with the moderately or heavily infected children reporting this symptom less frequently, which is difficult to interpret (Table 7.4). No recalled water contact pattern showed a significant odds ratio.

Table 7.4

Multivariate analysis to determine the most reliable questions predicting an *S. mansoni* infection of more than 100 eggs per gram stool (logistic regression modelling; n = 322 children; CI: confidence interval).

Variable	Adjusted odds ratio (95% CI)		Likelihood ratio statistics	p-value
Children surveyed				
Sex	1.08	(0.65-1.79)	0.97	0.755
Age group	**1.61**	**(1.09-2.38)**	**5.85**	**0.016**
Reported symptom				
blood in stool	**1.73**	**(1.03-2.91)**	**4.35**	**0.037**
bloody diarrhoea	0.58	(0.34-1-01)	3.75	0.053
Recalled water contact pattern				
Crossing rivers	1.31	(0.72-2.37)	0.77	0.379
Crossing river Sonbour	1.86	(0.95-3.66)	3.29	0.070
Crossing river Tchéorbour	1.16	(0.57-2.38)	0.17	0.676
Swimming/bathing	1.42	(0.71-2.83)	0.99	0.320
Swimming/bathing Sonbour	1.20	(0.61-2.36)	0.26	0.607
Swimming/bathing Tchéorbour	1.24	(0.63-2.45)	0.40	0.528

Diagnostic performance

The symptom 'blood in stool' showed only moderate sensitivity (44%, 95% CI: 38-50%) and moderate specificity (51%, 95% CI: 40-63%) for self-diagnosis of any *S. mansoni* infection. Both values increased slightly when emphasis was placed on self-diagnosis of moderate and heavy infections ($\geq$ 100 egp, Table 7.5).

Sensitivity and specificity values increased for moderately and heavily infected children, when compared to all infections, for both recalled water contact pattern 'crossing rivers' and 'swimming/bathing' (Table 7.5). Specificity values were consistently lower than sensitivity values. Probing for the location of water contact resulted in low sensitivities (25-48%) but high specificities (75-91%) for both infection thresholds (Table 7.5). The best single recalled water contact pattern for self-diagnosis of an *S. mansoni* infection was swimming/bathing in the river Sonbour with a moderate sensitivity of 42% (95% CI: 36-48%), a high specificity of 90% (95% CI: 80-95%), a high positive predictive value of 93% (95% CI: 86-97%) but a low negative predictive value of 32% (95% CI: 26-39%).

The diagnostic performance was only slightly improved by combinations of the different key questions that were determined by multivariate analysis (blood in stool, crossing rivers and swimming/bathing). The best diagnostic performance for self-diagnosis of an *S. mansoni* infection was found when a child gave at least one positive answer to the two questions swimming/bathing in the river Sonbour and swimming/bathing in the river Tchéorbour (sensitivity: 60%, 95% CI: 53-66%; specificity: 80%, 95% CI: 69-88%; positive predictive value: 91%, 95% CI: 85-95% and negative predictive value: 38%, 95% CI: 31-46%). The second best diagnostic performance was observed by the combination of swimming/bathing in the river Sonbour and crossing the river Tchéorbour (sensitivity: 58%, 95% CI: 51-64%; specificity: 82%, 95% CI: 71-89%; positive predictive value: 91%, 95% CI: 85-95% and negative predictive value: 37%, 95% CI: 30-45%).

Table 7.5

Diagnostic performance of reported blood in stool and the two most important recalled water contact patterns to predict any *S. mansoni* infection (first criteria) or all *S. mansoni* infections with more than 100 epg (second criteria; PPV: positive predictive value, NPV: negative predictive value).

Variable	Diagnostic performance in % (95% CI)			
	Sensitivity	Specificity	PPV	NPV
Criteria: all *S. mansoni* infections				
Reported blood in stool	44 (38-50)	51 (40-63)	75 (67-81)	22 (16-29)
Crossing rivers	61 (55-67)	47 (36-59)	79 (72-84)	27 (20-36)
Crossing river Sonbour	33 (27-39)	91 (81-96)	92 (84-96)	29 (24-36)
Crossing river Tchéorbour	25 (20-31)	91 (81-96)	90 (79-95)	27 (22-33)
Swimming/bathing	77 (71-82)	37 (26-49)	80 (74-85)	33 (23-44)
Swimming/bathing Sonbour	42 (36-48)	90 (80-95)	93 (86-97)	32 (26-39)
Swimming/bathing Tchéorbour	33 (28-40)	88 (78-94)	90 (82-95)	29 (23-36)
Criteria: all *S. mansoni* infections > 100 epg				
Reported blood in stool	52 (43-61)	60 (53-67)	48 (39-56)	64 (57-71)
Crossing rivers	70 (61-77)	52 (44-59)	50 (43-57)	71 (63-78)
Crossing river Sonbour	39 (31-48)	82 (75-87)	60 (49-70)	66 (60-72)
Crossing river Tchéorbour	26 (19-34)	82 (76-87)	50 (38-62)	61 (55-67)
Swimming/bathing	81 (73-87)	68 (61-75)	64 (56-71)	84 (77-89)
Swimming/bathing Sonbour	48 (39-57)	75 (68-81)	57 (47-66)	67 (61-74)
Swimming/bathing Tchéorbour	39 (30-48)	78 (72-84)	55 (45-66)	65 (58-71)

7.5   Discussion

The screening of 322 schoolchildren in a village in the western part of Côte d'Ivoire revealed a prevalence of *S. mansoni* infection of 76.4%, which confirms that this is an area highly endemic for *S. mansoni* (13, 18, 27). The survey also confirmed that hookworm, with a cumulative infection prevalence of 59.9%, is the most important geohelminth (29), whereas infections with *T. trichiura* and *A. lumbricoides* occurred only rarely.

Our conclusions about the prevalence of *S. mansoni* infection are based on examining four consecutive Kato-Katz thick smears. This is considered to be an accurate procedure to detect 'all' *S. mansoni* infections (25, 30). However, this method is only feasible in certain situations, as it is costly and requires skilled laboratory personnel. Furthermore, repeatedly bringing samples is likely to fatigue study subjects, so it is difficult to achieve complete data sets (18, 31).

There is a need for an alternative approach so that control programmes can make use of limited resources in the most effective way (32). Questionnaires addressed to lay people are one promising alternative. They have been successfully used at community level, for example to screen for *S. haematobium* (1-7, 10, 12). Systematic collection of information from lay people have also been found to be a reliable method to screen for high risk communities of a number of other diseases. The prevalence of dracunculiasis in a community can be assessed by the prevalence among schoolchildren (33). African onchocerciasis has been assessed by screening for 'leopard skin' (34), or by palpating skin nodules (35, 36) or by simply asking about the presence of nodules (37). Communities where lymphatic filariasis is important can be identified by talking to peripheral health workers and community key informants (38, 39).

For *S. mansoni* there is accumulating evidence from community- and hospital-based studies that blood in stool and/or bloody diarrhoea are consistently associated with infection (for review see Gryseels (40)). Therefore it was hoped that questionnaires asking about these symptoms might work for rapid screening. It was clear that other intestinal parasites (e.g. hookworms and amoebae) might cause the same symptom(s), so great care would be needed in the analysis and interpretation of the data (16, 17). In the present study, concurrent geohelminth infections were also investigated, but the analysis showed that they did not in fact confound the association between *S. mansoni* and reported blood in stool, which is in full agreement with our previous work in the same area (18).

In the present questionnaire study, however, we decided to explore additional questions other than reported blood in stool and bloody diarrhoea to try and improve the power of the questionnaire. Based on other studies, we also asked about a variety of different risk factors. These consisted of a series of questions on reported symptoms and diseases. The understanding of the terms used was assessed by focus group discussions beforehand. General and specific questions were also asked about water contact patterns, which were identified after discussion with community key informants and a walk through the village.

The reported symptom "blood in stool" showed only a moderate diagnostic performance with very similar sensitivity, specificity and positive and negative predictive values to those obtained from three neighbouring villages in a previous study (18). There were three general water contact patterns that were significantly associated with an increasing level of *S. mansoni* infections: crossing rivers, swimming/bathing and fishing with nets. However, logistic regression analysis revealed that only the more specific questions showed significant adjusted odds ratios: crossing the river Sonbour (3.9; 95% CI: 1.4-11.1); crossing the river Tchéorbour (3.9; 95% CI: 1.4-11.0); and swimming/bathing in the river Sonbour (3.3; 95% CI: 1.2-9.1). These three water contact patterns were characterised by high specificities and positive predictive values (90-93%), but low sensitivities and negative predictive values (25-42%). However, only a small proportion of *S. mansoni* infected children recalled having had those particular water contacts over the last month – though most of the non-infected children did not recall them at all. It is interesting to note that three Brazilian studies pursuing a comparable approach reported similar odds ratios and diagnostic performance for comparable water contact patterns (20, 22, 24). In one additional Brazilian study, children aged between 2 and 14 years who reported having had water contacts were 55.8 times more likely to be infected with *S. mansoni* (19).

Interestingly, the combination of different water contact patterns or the combination of the symptom "blood in stool" with different water contact patterns increased the diagnostic performance of our questionnaire only slightly. This is in contrast with a recent report from China, where a set of six risk factors was very reliable in predicting an infection with *S. japonicum* and revealed sensitivity and specificity values above 90% (26). There are various explanations for this. China has put a lot of effort into schistosomiasis control over the last decades, and high risk communities have been treated repeatedly with antischistosomal drugs (41). Thus, people have been exposed to schistosomiasis control for a long time, and this may have resulted in a clearer disease perception. This is the likely explanation for a previous treatment history of schistosomiasis being among the risk factor predicting an infection with *S. japonicum*. In many areas in Africa, treatment has never been carried out on a large scale, so a question about previous treatment would not have been useful.

To summarize; recalled water contact patterns were better predictors than questions about symptoms for an infection with *S. mansoni*. However, the diagnostic performance was still only moderate, and these questionnaires administered to young schoolchildren cannot be recommended for self-diagnosis of *S. mansoni* infection. However, it might be possible to use questionnaires administered to adolescence and adults (including caretakers of children) as they are likely to have a clearer disease perception. If this proves to be successful, questionnaires could be developed for identifying individuals and communities with *S. mansoni* infection. The benefit of having such a screening tool would be considerable, as *S. mansoni* continues to be an important public health threat in most countries of sub-saharan Africa.

7.6   Acknowledgements

Author's addresses: Jürg Utzinger, Christian Lengeler and Marcel Tanner, Swiss Tropical Institute, PO Box, CH-4002 Basle, Switzerland. Eliézer K. N'Goran, Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire.

Reprint requests: Christian Lengeler, Swiss Tropical Institute, Department of Public Health and Epidemiology, PO Box, CH-4002 Basle, Switzerland.

Tel: + 41 61 284 82 83; Fax: + 41 61 271 79 51; e-mail: christian.lengeler@unibas.ch

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8 **Simple school questionnaires can map both *Schistosoma mansoni* and *Schistosoma haematobium* in the Democratic Republic of Congo**

Christian Lengeler [1,*], Jérôme Makwala [2], Dennis Ngimbi [3], Jürg Utzinger [1]

1 Swiss Tropical Institute, Department of Public Health and Epidemiology, P.O. Box, CH–4002 Basle, Switzerland

2 Département de Démographie, Université de Kinshasa, B.P. 20.805 CCIZ, Kinshasa Gombe, Democratic Republic of Congo

3 Département de Parasitologie, Université de Kinshasa, B.P. 20.805 CCIZ, Kinshasa Gombe, Democratic Republic of Congo

* Corresponding author

Tel   (+41 61) 284 82 21
Fax   (+41 61) 271 79 51
e-mail   christian.lengeler@unibas.ch

8.1   Abstract

The use of self-administered questionnaires has been shown in different African countries to be inexpensive and reliable for the rapid identification of communities at highest risk of urinary schistosomiasis. For intestinal schistosomiasis due to *S. mansoni* there is a clear need for a similar approach. We report the results from a large-scale study undertaken in the western part of the Democratic Republic of Congo (DRC, formerly Zaïre).

Within 4 weeks questionnaires were correctly completed in 136 out of 160 schools (85%). In 57 of these schools children were screened for infections with schistosomes and geohelminths. The prevalence of "schistosomiasis" as reported in the questionnaires showed the best correlation with the prevalence of *S. mansoni* infections (r = 0.77, p < 0.0001). Calculations of the diagnostic performance of reported "schistosomiasis" to detect schools with a high risk of intestinal schistosomiasis gave positive predictive values of 87% and 62%, and negative predictive values of 74% and 87% for moderate and high infection thresholds, respectively. Reported "blood in stool" was another useful indicator for intestinal schistosomiasis. Reported "blood in urine" showed the best correlation with urinary schistosomiasis (r = 0.75, p < 0.001) and the positive predictive values were 81% and 50%, and the negative predictive values were 89% and 95% for moderate and high infection thresholds, respectively. We conclude that school children in DRC have a distinct perception of intestinal and urinary schistosomiasis and that questionnaires could be useful to identify high risk schools for both parasites.

Keywords: Schistosomiasis – *Schistosoma haematobium* – *S. mansoni* – school questionnaires – Democratic Republic of Congo

8.2   Introduction

Schistosomiasis is a widespread parasitic infection of man, of great importance in tropical and subtropical environments, with an estimated total of 200 million people infected (WHO, 1993; Davis, 1996). Disease transmission is influenced by numerous factors, such as intermediate host snail distribution, patterns of environmental contamination with human excreta, water contact by man, and host-parasite relationship (Wilkins, 1987). The disease is expected to increase in importance for three main reasons: (i) the growing number of irrigation systems, (ii) the construction of dams and man-made lakes for hydroelectric power production and (iii) civil strife and war, which contribute to additional human migration and disruption of health services and control programmes (Mott et al., 1995). At present the distribution of schistosomiasis is very focal in many areas (Webbe and Jordan, 1993; Malone et al., 1997), and control is often given a low priority because it represents a serious problem only in certain localities. There is therefore a great need for rapid but accurate identification of the areas at highest risk of human schistosomiasis in order to better target control activities (Vlassoff and Tanner, 1992).

The use of self-administered questionnaires to identify communities at high risk for urinary schistosomiasis proved to be effective in several African countries with different levels of endemicity (Lengeler et al., 1991a, b; Red Urine Study Group, 1995; Ansell et al., 1997; N'Goran et al., 1998). The success of the questionnaire approach was explained by the fact that urinary schistosomiasis is generally well recognized by the presence of blood in urine, which is a sensitive and specific symptom. Comparison with standard parasitological examinations revealed that the questionnaire approach was highly cost-effective (Lengeler et al., 1991a, b, c, 1992; Red Urine Study Group, 1995; Siziya et al., 1996). Consequently, the approach was recommended to form the first step of community-based morbidity control programmes and the WHO published guidelines for use by district health officers (Chitsulo et al., 1995).

For intestinal schistosomiasis due to *S. mansoni*, which is becoming in many areas more important than urinary schistosomiasis (Abdel-Wahab et al., 1979; Stelma et al., 1993; Mott et al., 1995; Picquet et al., 1996), there is a growing need for rapid and low-cost screening at community level. There has already been considerable research to identify diagnostic signs and symptoms that might identify reliably intestinal schistosomiasis cases. It was found that diarrhoea, especially bloody diarrhoea, and blood in the stools were significantly associated with *S. mansoni* infections in most areas (see Gryseels 1992 for a review). In a series of studies it was found that blood in stool was consistently more often reported among *S. mansoni* infected children than controls (Sukwa et al., 1985; Proietti and Antunes, 1989; Lima e Costa et al., 1991; Hailu et al., 1995; Booth et al., 1998; Utzinger et al., 1998). These results were promising and formed the basis for the development and validation of the questionnaires approach. Since the distribution of *S. mansoni* and *S. haematobium* is overlapping in many African countries (Doumenge et al., 1987), the ability to detect both species in a single step will be crucial for country-level screening.

The work presented here was undertaken in 1991-1992 in western Democratic Republic of Congo (DRC), at a time when it was still called Zaïre. It was part of the WHO-supported multicountry study to evaluate the feasibility and usefulness of the *S. haematobium* questionnaire (Red Urine Study Group, 1995). Previous studies conducted in the area (Mandahl-Barth et al., 1974; Doumenge et al., 1987) and health statistics available before the study showed that intestinal schistosomiasis was also present in the area. Therefore, in DRC the study was considered to be an ideal opportunity to evaluate the performance of questionnaires to identify not only high risk communities for urinary schistosomiasis but also those at high risk for intestinal schistosomiasis. Emphasis was put on the interaction of the two species in terms of disease perception, and on the ability of the questionnaire approach to discriminate between the two.

8.3   Materials and Methods

Study area

The study was carried out in the town of Matadi and the administrative zone of Songololo, located in the narrow stretch of land between the Zaïre River and the Angolan Republic, west of Kinshasa (Figure 8.1). The area covers approximately 9,000 km^2. At the time of the study, the total population was estimated at 380,000 people, of whom about 26% were Angolan refugees. There are two distinct seasons: a rainy season of 8-9 months lasting from October to May and a shorter dry season in between. The hydrography is dominated by rivers flowing south-north, from Angola into the lower-lying Songololo area. Further details of the study area are provided elsewhere (Red Urine Study Group, 1995). Major civil troubles, a national strike, difficult access to certain areas, and moving of key administrative personnel during the implementation and validation phases were responsible for delaying the completion of the study until September 1992.
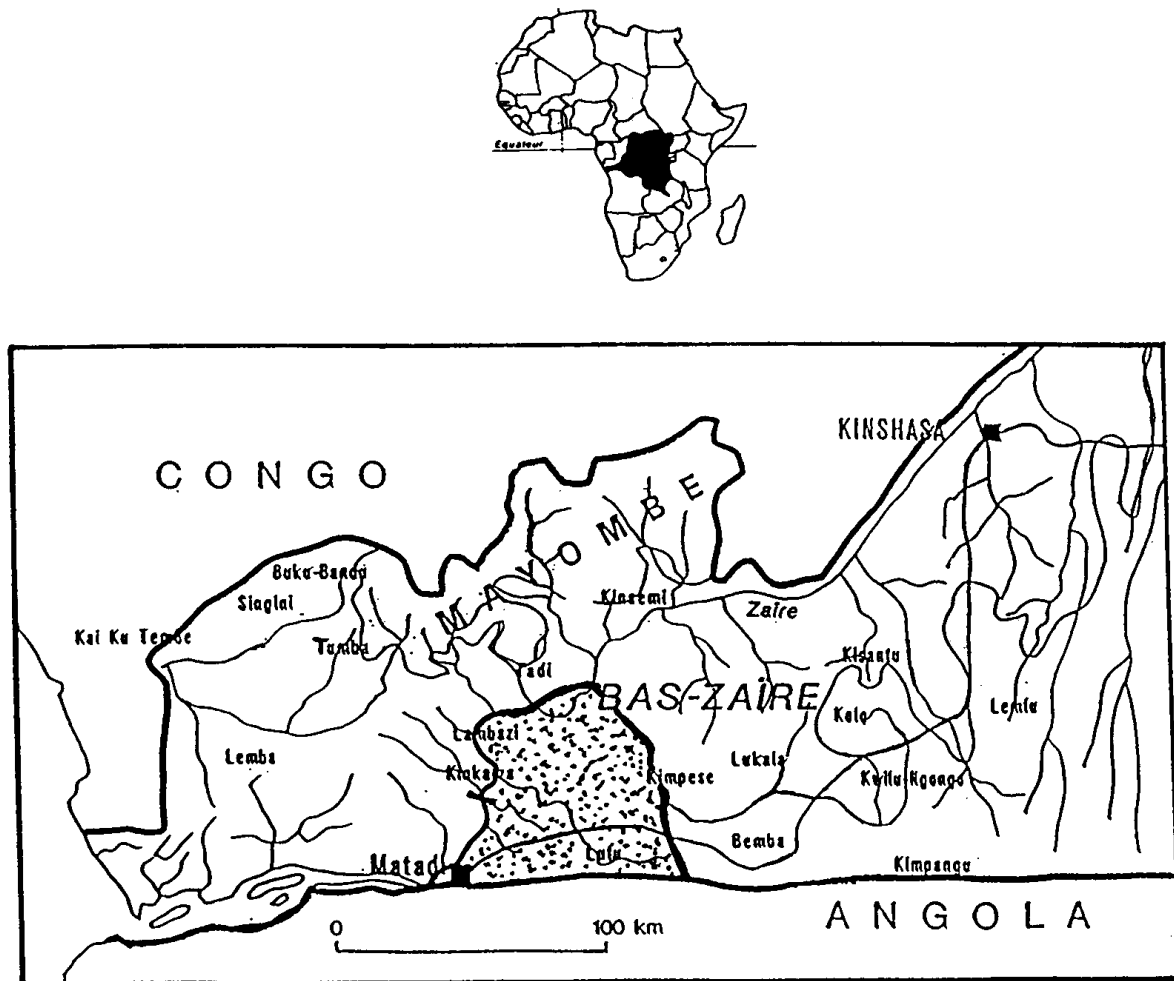

Figure 8.1

Map of the study area with the town of Matadi and the administrative zone of Songololo (dots) in the western part of the Democratic Republic of Congo (formerly Zaïre).

Study design

The original English version of the schoolchildren's questionnaire used in Tanzania (Lengeler et al., 1992) was translated into French and thoroughly pre-tested until it was well understood. The key questions for our purpose were: "did you have blood in the stool during the last month" ('sang dans les selles'), "blood in urine" ('sang dans les urines') and "schistosomiasis" ('bilharziose'). For the final version of the questionnaire see Red Urine Study Group (1995). In February 1991, the questionnaire was administered through the existing administrative channels to all the primary schools of the study area (n = 160). The head teachers of standard 4-6 classes were asked to interview all their children individually and to return the filled-in questionnaires as soon as possible.

For the parasitological validation of the questionnaire results, a simple random sample of 60 schools was drawn from among the 136 schools which returned the questionnaires. However, only 57 schools could be visited because of the difficult circumstances under which the study was carried out. Between May and August 1991, a laboratory team went to all these schools and screened approximately 100 schoolchildren per school for intestinal schistosomiasis and geohelminths, using a single Kato-Katz thick smear. Originally, it was planned to screen for the presence of microhaematuria (an indirect indicator of urinary schistosomiasis) at the same time, but the first batch of reagent sticks had been stolen at the Kinshasa airport. As a result, the testing could not be done at the same time and was only completed one year later.

Biomedical testing methods and treatment of infected children

Plastic containers (volume: 250 ml) were distributed in all the 57 selected schools, and the children were asked to provide a small portion of their morning stools the following day. From each stool specimen, a single 42 mg Kato-Katz thick smear was processed according to Katz et al. (1972). The smears were allowed to clear overnight and read under a microscope at low magnification. The number of *S. mansoni* eggs was counted and the number of eggs per gram of stool calculated. In 40 of those schools, the presence of *Ascaris lumbricoides* and *Trichuris trichiura* was also assessed. Hookworms were also counted but since a single Kato-Katz test with a long clearing time is very insensitive for this parasite the results were not used.

Infections with *S. haematobium* were indirectly assessed by the presence of microhaematuria using reagent stick testing (Sangur-Test, Boehringer Mannheim, Germany), which has been demonstrated to be a reliable indicator (Mott et al., 1985). This was done approximately one year after stool analysis and before praziquantel treatment for the reasons given above. Care was taken to test the same children who were initially screened for intestinal schistosomiasis. This was possible because the original class lists were available. However, since a large proportion of children did not frequent the same schools any longer, it was only possible to obtain reagent stick results from 43% of the children in 49 of the 57 schools in which the Kato-Katz testing had been done. Urine specimens were collected between 10.00 and 14.00 hours in

small plastic containers. They were stirred and reagent sticks were briefly dipped. After approximately 60 seconds the colour change was read according to the manufacture's instructions and results were written down in four categories: negative, 1+, 2+ or 3+.

Children who excreted *S. mansoni* eggs in their stools and/or had a positive reagent stick result were treated with a single oral dose of praziquantel at the recommended standard dose of 40 mg per kg body weight (WHO, 1993). Initially, it was planned that positive children would be referred to a health centre and treated there. This proved to be very difficult under the given political circumstances and the laboratory team decided to treat the children directly in the schools, immediately after the reagent stick testing.

Data analysis

All data derived from the questionnaires and the parasitological surveys were entered and analysed in EpiInfo (version 5.01, USD Inc. Stone Mountain, USA). Extensive consistency and range checks were performed and abnormalities were sorted out by referring to the original pro-formas. Positivity rates were computed for the reported symptoms (recall period: one month): 'schistosomiasis', 'blood in urine' and 'blood in stool'. Point prevalences of infection were calculated for *S. mansoni* (assessed by positive egg count in stool with a Kato-Katz examination), *S. haematobium* (indirectly assessed by microhaematuria $\geq 1+$) and geohelminths.

Simple and multiple linear regression analysis were performed at school level to calculate the correlation between the prevalences of reported symptoms and the infection prevalences for *S. mansoni* and *S. haematobium*. Partial correlation coefficients were calculated according to Snedecor and Cochrane (1968).

The diagnostic performance of the two most promising symptoms for each parasite was calculated from the data aggregated at school-level. Firstly, the schools were classified according to whether they were at "high risk" or not. This was done for two different thresholds according to Montresor et al. (1998): moderate ($\geq 20\%$) and high prevalence ($> 50\%$). For each of these two risk thresholds we determined the appropriate questionnaire positivity cut-off (i.e. the response rate above which the given school is considered as "positive" according to the questionnaire) by determining the questionnaire positivity value coresponding to 20% and 50% *S. mansoni* or *S. haematobium* prevalence using the regression lines in Figures 8.2 and 8.3. This cut-off was of course different when trying to identify schools with a moderate risk (over 20% parasitological prevalence) or a high risk (over 50% parasitological prevalence).

From the aggregated school data the following 2x2 table could be constructed:

Sign/symptom	Negative schools (*S.m./S.h.* prevalence rate below threshold)	Positive schools (*S.m./S.h.* prevalence rate over threshold)
Response rate in schools below the diagnostic cut-off value ("negative")	**A**	**B**
Response rate in schools above the diagnostic cut-off value ("positive")	**C**	**D**

Sensitivity: D / B+D   Specificity: A / A + C

Positive predictive value: D / C + D   Negative predictive value: A / A + B

As a check, the sensitivity and specificity values were combined with the proportion of schools at "high-risk" (the "prevalence" data) and the predictive values were re-calculated using the formulas of Baye's theorem in a generic spreadsheet. Confidence intervals were calculated for all diagnostic performance based on the binomial distribution.

Since names were not available on the questionnaires it was impossible to link the questionnaire responses to the parasitological results of the same child, and therefore no analysis could be performed at the individual level.

8.4   Results

Operational results

Within a period of 4 weeks completed questionnaires were returned from 136 out of 160 schools (85.0%). Overall, a total of 19,362 schoolchildren were interviewed. Their mean age was 12.5 ± 1.8 years and the sex-ratio between males and females was 1.3:1. The average number of children interviewed per school was 142 ± 50 (range: 22-210).

From these136 schools, 60 were randomly selected for parasitological validation by the laboratory team. However, owing to the difficult circumstances during the survey period, only 57 could be visited. A total of 5,806 children provided stool specimens to assess infection with intestinal schistosomiasis and geohelminths. The mean age of these children was 13.3 ± 1.9 years, the male:female sex ratio was 1.3:1, and the mean number of children per school was 102 ± 12 (range 45-123). The overall infection prevalence of *S. mansoni* was 31.2% with a large range (0-89.7%) between individual schools (Table 8.1). The questionnaires revealed that having "schistosomiasis", "blood in stool" and "blood in urine" during the last month was

reported by 22.0%, 15.8% and 11.2% of the children, respectively (Table 8.1). Point prevalence rates of geohelminths and microhaematuria are also given in Table 8.1. Interestingly, mixed infections of *S. mansoni* and *S. haematobium* were not frequent: 8.2% (Table 8.1).

Table 8.1

Overall questionnaire and parasitological results (Democratic Republic of Congo).

	# positive	# tested	Prevalence in % (95% CI)
Questionnaire positivity rates (n=57 schools)			
'Having schistosomiasis'	1814	8244	22.0 (21.1-22.9)
'Blood in stool'	1301	8244	15.8 (15.0-16.6)
'Blood in urine'	925	8244	11.2 (10.5-11.9)
Kato-Katz thick smear results			
S. mansoni [a]	1813	5806	31.2 (30.0-32.4)
Ascaris lumbricoides [b]	1741	4032	43.2 (41.6-44.7)
Trichuris trichiura [b]	1544	4032	38.3 (36.8-39.8)
Reagent stick testing results (n=49 schools)			
microhaematuria (*S. haematobium*)	505	2495	20.2 (18.7-21.9)
Mixed infections *(S. mansoni/S. haematobium)*			
Overall rate of mixed infections	204	2495	8.2 (7.1-9.3)

a) n = 57 schools   b) n = 40 schools

Questionnaire results and parasitological surveys

The comparisons between the school prevalence rates for *S. mansoni* infections and the prevalences of reported "schistosomiasis" and reported "blood in stool" are shown in Figures 8.2a and 8.2b. There was a strong positive correlation between infection prevalences of *S. mansoni* and the reported frequency of both symptoms. The prevalence of reported "schistosomiasis" showed a highly significant correlation with *S. mansoni* infections ($r = 0.77$, 95% CI: 0.64-0.86, $p<0.001$). The correlation coefficient between *S. mansoni* and reported blood in stool was 0.34 (95% CI: 0.09-0.55, $p<0.01$).

Reported "blood in urine" and reported "schistosomiasis" correlated significantly with the prevalence of microhaematuria (Table 8.2). Reported "blood in urine" showed a better correlation with microhaematuria (crude correlation coefficient $r = 0.75$) than with reported "schistosomiasis" (crude correlation coefficient $r = 0.42$). When these results were controlled for *S. mansoni* infections by a multiple regression technique, the adjusted correlation coefficients remained essentially the same (0.42 vs 0.44 for "schistosomiasis", 0.75 vs 0.74 for

"blood in urine" - Table 8.2). In other words, the relation between reported "blood in urine" or reported "schistosomiasis", and measured microhaematuria was not confounded by the infection status with *S. mansoni*.
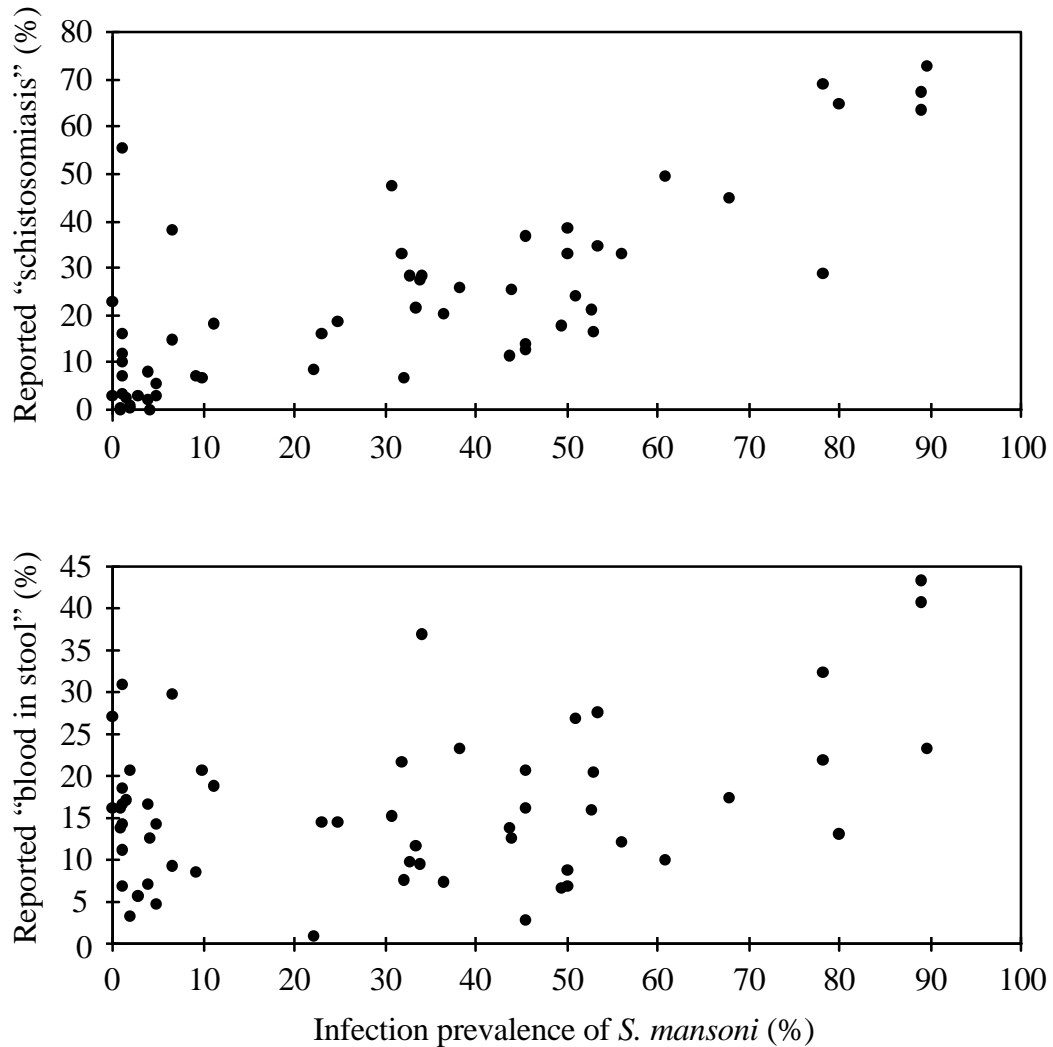

Figure 8.2

Association between the infection prevalence of *Schistosoma mansoni* and reported "schistosomiasis" (a) and reported "blood in stool" (b) in 57 schools.

When the correlation between reported "blood in stool" and *S. mansoni* infections was controlled for the microhaematuria results, the correlation coefficients did not change (0.34 vs 0.33 - Table 8.2). On the other hand, when the correlation between reported "schistosomiasis" and *S. mansoni* infections was controlled for the microhaematuria results, the correlation coefficient for reported "schistosomiasis" was reduced from 0.77 to 0.61. Although this effect is not very important, it did indicate that an infection with *S. haematobium* was to a small extent a confounding factor for the association between reported "schistosomiasis" and *S. mansoni* infection status.

Additional controlling for *A. lumbricoides* and *T. trichiura* infections revealed that these parasites did not act as confounding factors for any of the relations.

Table 8.2
Crude and adjusted correlations between questionnaire results and parasitological findings (partial correlation coefficients from Snedecor & Cochrane, 1968). ns = not statistically significant.

	Reported symptom		
	Schistosomiasis	Blood in stool	Blood in urine
Correlations with Kato-Katz results: *S. mansoni* (n = 57 schools)			
Crude correlation	r = 0.77 p<0.0001	r = 0.34 [a)] p<0.02	r = 0.23 ns
Corrected for reagent stick results	r = 0.61 p<0.0001	r = 0.33 [a)] p<0.02	r = 0.13 ns
Correlations with reagent stick results: *S. haematobium* (n = 49 schools)			
Crude correlation	r = 0.42 p<0.01	r = 0.08 ns	r = 0.75 p<0.0001
Corrected for Kato-Katz results	r = 0.44 p<0.01	r = 0.02 ns	r = 0.74 p<0.0001

a) Unchanged after additional controlling for *Ascaris lumbricoides* and *Trichuris trichiura*.

Diagnostic performance of the questionnaire

The diagnostic performance of reported "schistosomiasis" and reported "blood in stool" to detect high risk schools for *S. mansoni* at two different disease detection thresholds is shown in Table 8.3. The detection thresholds represent the minimum prevalence level at which a school would be labelled as 'high risk' according to the criteria of Montresor et al. (1998). For *S. mansoni* prevalence detection, reported "schistosomiasis" showed moderate (74.1%) and high (88.6%) negative predictive values at the two detection thresholds. Reported "blood in stool" showed a weaker diagnostic performance, but the negative predictive value was still 87.2% at the higher detection threshold. The negative predicitve value is especially important

for diagnostic screening, because it allows to safely exclude schools which do not have a major schistosomiasis problem.

The diagnostic performance of reported "blood in urine" for the identification of high risk schools for *S. haematobium* infections was found to be good in this survey (Table 8.4), confirming results from other African studies.

Table 8.3

Diagnostic performance of reported "schistosomiasis" and reported "blood in stool" to identify schools at a high risk for *S. mansoni* infections, at two different detection thresholds (20% and 50% parasitological prevalence rate). Proportion of positive schools were 58% (moderate risk) and 25% (high risk). CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

Reported symptom	*S. mansoni* detection threshold	Questionnaire positivity rate	Diagnostic performance in % (95% CI)			
			Sensitivity	Specificity	PV +	PV −
Schistosomiasis	Moderate prevalence (> 20%)	17.2	79 (61-90)	83 (62-95)	87 (68-96)	74 (53-88)
	high prevalence (> 50%)	33.7	62 (32-85)	89 (75-96)	62 (32-85)	87 (75-96)
Blood in stool	Moderate prevalence (> 20%)	15.1	49 (31-66)	50 (30-70)	57 (37-75)	41 (72-95)
	High prevalence (> 50%)	18.5	62 (32-85)	77 (62-88)	44 (22-69)	87 (72-95)

Table 8.4

Diagnostic performance of reported "schistosomiasis" and reported "blood in urine" to identify schools at a high risk for *S. haematobium* infections, at two different detection thresholds (20% and 50% parasitological prevalence rate). Proportion of positive schools were 40.0% (moderate risk) and 12% (high risk). CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

| Reported symptom	*S. haematobium* Detection threshold	Questionnaire positivity rate	Diagnostic performance in % (95% CI)			
			Sensitivity	Specificity	PPV	NPV
Schistosomiasis	Moderate prevalence (> 20%)	22.8	65 (41-84)	69 (49-84)	59 (37-79)	74 (53-88)
	High prevalence (> 50%)	34.9	80 (30-99)	84 (69-93)	36 (12-68)	97 (85-100)
Blood in urine	Moderate prevalence (> 20%)	12.1	85 (61-96)	86 (67-96)	81 (57-94)	89 (71-97)
	High prevalence (> 50%)	24.1	60 (17-92)	93 (80-98)	50 (14-86)	95 (83-99)
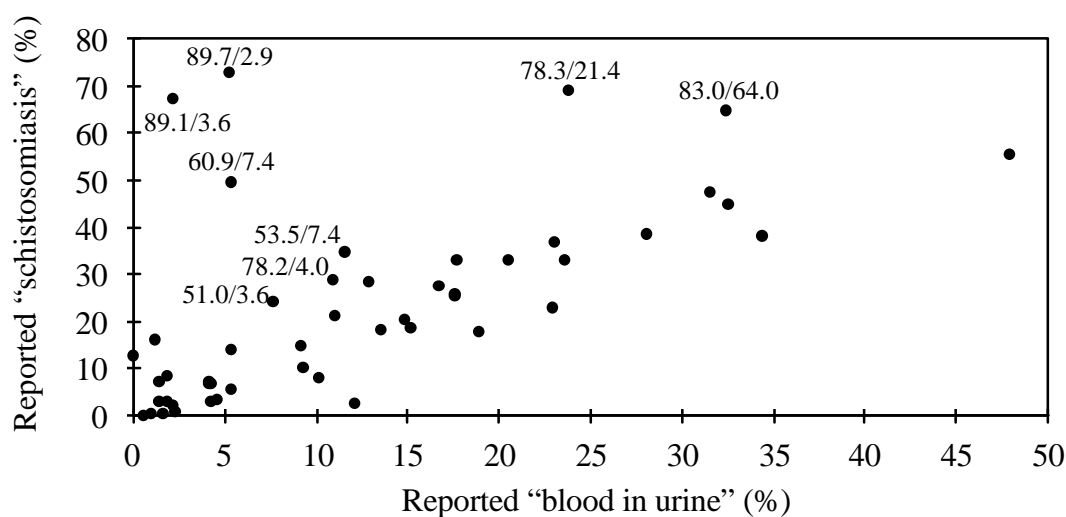
Figure 8.3

Association between reported "blood in urine" and reported "schistosomiasis" in 49 schools. Numbers above pointes: infection prevalence of *S. mansoni* (assessed by Kato-Katz thick smear) / infection prevalence of *S. haematobium* (assessed by reagent stick testing).

8.5 Discussion

Over the last decade, a considerable amount of experience has been collected with the use of questionnaires distributed through an existing administrative channel. As peak intensity of schistosomiasis infections typically occurs in the age-group 10 to 14 years (Webbe and Jordan, 1993), schools are the logical place for assessing the prevalence and intensity of infections and setting up treatment programmes. For urinary schistosomiasis questionnaires allowed to identify rapidly and at low-cost the schools with the highest infection prevalences. These results were confined by our work.

In a large number of previous studies the collaboration with the school authorities was excellent with return rates for questionnaires ranging between 75% and 100% (Lengeler et al., 1991a, b, c; Red Urine Study Group, 1995; Ansell et al., 1997; N'Goran et al., 1998). Despite the fact that the present study in the Democratic Republic of Congo (formely Zaïre) was carried out during a period of major civil disturbance, a national strike and moving of key administrative personnel, the return rate of correctly completed questionnaires was high (85%). This clearly emphasizes the feasibility of using questionnaires targeted at schools, even in areas where there is political unrest. Schools are generally well organized and can to some extent be self-supporting with the help of children's parents, and they often continue to be operational under difficult circumstances. They provide therefore a suitable infrastructure for reaching infected individuals. It was recently recommended that school teachers could play an increasingly important role in schistosomiasis control and also other helminth control programmes (Magnussen et al., 1997; Ansell et al., 1997).

It has been shown that questionnaires might be useful for the rapid identification of schools at a high risk for *S. mansoni* infections (Hailu et al., 1995; Utzinger et al. submitted) and this is also the case at individual level (Utzinger et al., 1998). In the present study, school infection rates with *S. mansoni* correlated best with reported "schistosomiasis". The correlation between *S. mansoni* infections and reported "schistosomiasis" was slightly reduced after additional controlling for microhaematuria, which is a sensitive indicator for *S. haematobium* infections (Mott et al., 1985; Lengeler et al., 1993). It indicated that reported "schistosomiasis" did also include to some extent *S. haematobium* infections. Given the low level of mixed infections this was not a significant factor in our study. However, it might be more important in areas where the infection overlap is more important.

This raised the issue of how best to discriminate between *S. haematobium* and *S. mansoni* infections with the questionnaire approach in areas where both parasites occur. Pooling the results from studies conducted in 9 different countries, it could be shown that in *S. haematobium* areas there is a very good correlation between reported "blood in urine" and reported "schistosomiasis": r = 0.84-0.94, p<0.0001 (Lengeler et al. 1991a; Red Urine Study Group 1995; N'Goran et al., 1998). Our study confirmed this but we also found some schools in which a high proportion of children reported "schistosomiasis" while only few of those children reported "blood in urine". Detailed analysis in these schools showed high infection

prevalences with *S. mansoni* but only few children positive for microhaematuria; these schools appear as outlyers in Figure 8.3.

Relying only on questionnaire results, a high prevalence of reported "schistosomiasis" but a low prevalence of reported "blood in urine" is therefore likely to indicate a predominance of *S. mansoni* infections in that school. We believe that this divergence between reported "blood in urine" and reported "schistosomiasis", which is not found in a *S. haematobium* focus, might allow to identify selectively *S. mansoni* foci. In areas where both parasites occur but where they are not overlapping at the village level (for example if the intermediate host snails do not co-exist in the main transmission sites), this finding might be useful for the identification of high risk schools for *S. mansoni*. However, in areas in which both parasites co-exist in the same locality (as in our study area, data not shown), the identification of individual high risk schools is less straight forward. However, the discrepancy between reported "blood in urine" and reported "schistosomiasis" can be used to signal the presence of intestinal schistosomiasis and it may indicate areas where detailed investigations might be warranted.

A consistent association was found between reported "bloody stool" and infections with *S. mansoni* in different endemic areas in Africa and also in Brazil. However, the sensitivity of this symptom was generally found to be low at individual level (Sukwa et al., 1985; Proietti and Antunes, 1989; Lima e Costa et al., 1991; Hailu et al., 1995; Booth et al., 1998; Utzinger et al., 1998; Utzinger et al. submitted). The results of the present study confirmed the significant association between reported "blood in stool" and infection prevalences of *S. mansoni* at school level, although the diagnostic performance was only moderate. A multivariate analysis showed that this correlation remained unchanged after controlling for *S. haematobium*, and also other intestinal parasites. This may indicate that reported "blood in stool" is rather uniquely associated with intestinal schistosomiasis and it confirms recent findings in Côte d'Ivoire (Utzinger et al., 1998) and Tanzania (Booth et al., 1998).

In our study the return rate of the questionnaires was high (over 85%) and the random sampling of the schools provided a good basis for assessing the questionnaire's performance. The major limitation of the school lied in the fact that the reagent stick testing was carried out one year after the questionnaire and the Kato-Katz assessments. This was very unfortunate but it was beyond the control of the investigators. We can only guess whether this biased our results but we take heart from two significant facts. Firstly, our results for *S. haematobium* were carried out in the frame of a standardized multi-country study (Red Urine Study Group 1995) and our results were fully in line with those of the other participating countries. This is an indication that the correlation between questionnaires and reagent stick testing was not affected in a major way. Secondly, a comparison of the questionnaire positivity rates in (i) all the schools (n=136), (ii) the schools in which the Kato-Katz examinations were done (n=57) and (iii) the school in which only reagent stick testing was done (n=49) showed only minor variations for the three major questions: "schistosomiasis": 23% vs 18% vs 23 %, "blood in stool": 16% vs 16% vs 15%, and "blood in urine": 11% vs 9% vs 12%. This might be an indication that there was not a major systematic bias as a result of the dropout problem.

It was not clear how children perceived and recognized intestinal schistosmiasis as a disease ("bilharziose"), although informal discussions revealed that many children had been treated before and that this played a role in their recall. Treatment history had already been found to be important in two subsequent studies in Brazil and China (Barreto et al. 1993; Zhou et al. 1998). In any case, it would be interesting to examine in more detail this question of the children's perception of the disease since it might be a key to improving the questionnaire approach. In Zaïre (now DRC), simple school questionnaires were able to identify schools at highest risk for both urinary and intestinal schistosomiasis and these findings might be important for large scale screening of schistosomiasis in Africa.

8.6   Acknowledgements

8.7   References

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9   Intestinal amoebiasis, giardiasis and geohelminthiases: their association with other intestinal parasites and reported intestinal symptoms

J. Utzinger [1,2], E.K. N'Goran [2,3], H.P. Marti [1], M. Tanner [1] and C. Lengeler[1,$]

1   Swiss Tropical Institute, Department of Public Health and Epidemiology, PO Box, CH-4002 Basle, Switzerland

2   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   Laboratoire de Biologie Animale, UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

$ Corresponding author
       Tel: + 41 61 284 82 21
       Fax: + 41 61 271 79 51
       e-mail: christian.lengeler@unibas.ch

9.1   Summary

In order to determine reported signs and symptoms that may predict an intestinal parasitic infection, 241 schoolchildren in western Côte d'Ivoire were interviewed with a simple questionnaire and their stool specimens were examined over several consecutive days. Special emphasis was placed on (1) assessing infections by *Entamoeba histolytica/E. dispar*, *Giardia lamblia* and by intestinal worms (2) looking for associations between these parasites, and (3) looking for associations between these parasites and commonly perceived intestinal signs and symptoms. Complete questionnaire results, intestinal helminth infections derived from four Kato-Katz thick smears, and intestinal protozoa infections assessed on a single day by a formalin-ether concentration procedure were obtained from 209 children (87%).

A logistic regression modelling approach showed that an infection with *E. histolytica/E. dispar* was significantly associated with an *Entamoeba coli* infection. However, for *G. lamblia*, hookworm and *Ascaris lumbricoides*, no association was found between any of these parasites and other intestinal parasites. In a multivariate analysis reported diarrhoea was the only symptom positively associated with an *E. histolytica/E. dispar* infection (p = 0.028). Its diagnostic performance showed a low sensitivity (28%), a high specificity (85%) and moderate positive and negative predictive values (52% and 67%, respectively). Surprisingly, reported 'turning stomach' was less often reported by children infected with *G. lamblia* (borderline significance, p = 0.057). It is concluded that reported diarrhoea could be a symptom worth exploring further for the rapid identification of schoolchildren infected with *E. histolytica/E. dispar*.

Key words: Amoebiasis – *Ascaris lumbricoides* – Côte d'Ivoire – Disease perception – *Entamoeba histolytica/E. dispar* – Geohelminthiasis – *Giardia lamblia* – Giardiasis – Hookworm – Intestinal parasites

9.2   Introduction

Amoebiasis caused by *Entamoeba histolytica* is believed to affect about 480 million people worldwide, and leads approximately to 40,000-110,000 deaths per year (WALSH, 1986; WHO, 1997). It has long been known that the majority of infected individuals are asymptomatic and that only about 10% develop disease (FARTHING *et al.*, 1996). The accumulation of recent biochemical, immunological and genetic data revealed that *E. histolytica* and *E. dispar* are two morphologically identical protozoan species (DIAMOND & CLARK, 1993). It is now generally accepted, that only *E. histolytica* can cause invasive intestinal and extra-intestinal disease (WHO, 1997).

Giardiasis is a common protozoan infection of the intestinal tract and occurs worldwide. While there has been a long-lasting debate on the pathogenic significance of *Giardia lamblia* there is now evidence that this parasite can cause both acute and persistent diarrhoea as well as vitamin and nutrient malabsorption, and that it may be responsible for growth and development retardment in children (ADAM, 1991; FARTHING, 1996).

Several recent studies investigated the aetiology of acute and chronic diarrhoea and demonstrated the pathogenic potential of *E. histolytica*/*E. dispar* (CHATTERJEE *et al.*, 1989; SHETTY *et al.*, 1990) and *G. lamblia* (SHETTY *et al.*, 1990; CHUNGE *et al.*, 1992). In a recent case-control study HENRY *et al.* (1995) found that an infection with *E. histolytica*/*E. dispar* was statistically associated with chronic diarrhoea. YOUNES *et al.* (1996) studied 60 patients with persistent or recurrent diarrhoea and identified *G. lamblia* as the most prevalent pathogen responsible for diarrhoea in 23.3% of these cases, followed by *E. histolytica* in 21.6% of the cases. The study by CHUNGE *et al.* (1992) also investigated the association between intestinal parasitic infections, unformed stool and reports of diarrhoea; they found significant correlations between the occurrence of both *E. histolytica* and *G. lamblia* and reported diarrhoea. The more severe forms of amoebiasis and giardiasis are rare and will not be considered here.

Infections with other intestinal parasites may also cause intestinal signs and symptoms. This is especially the case with the geohelminths: *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms (*Necator americanus*, *Ancylostoma duodenale*) that can cause intestinal symptoms beside having other detrimental effects - such as vitamin malabsorption and contributing to anaemia (BUNDY, 1986; ADEDOYIN *et al.*, 1990; SHERCHAND *et al.*, 1996; TSHIKUKA *et al.*, 1996). On the other hand there is ample evidence that infections due to *Schistosoma mansoni* (classified here as intestinal parasite because of the excretion of eggs in the faeces) can cause (bloody) diarrhoea, blood in stool, abdominal pain and colicky cramps (reviewed by GRYSEELS, 1992).

We report a study that looked at the reliability and diagnostic performance of simple reported signs and symptoms for the identification of intestinal parasite infections. The marked relationship between reported blood in stool and intestinal schistosomiasis caused by *S. mansoni* is described elsewhere (UTZINGER *et al.*, 1998). In the present paper, emphasis is placed on *E. histolytica*/*E. dispar*, *G. lamblia*, hookworm and *A. lumbricoides*. A multivariate analysis strategy using logistic regression was used to investigate the associations between the different intestinal parasites and to assess the most reliable signs and symptoms that may indicate intestinal protozoa and helminth infections.

9.3   Materials and Methods

Study area and population surveyed

The study was carried out near the town of Man in western Côte d'Ivoire between March and June 1997. All schoolchildren attending standard 4-6 from three neighbouring rural primary schools were enrolled. The objectives of the study were discussed with the village chiefs and the school directors and after obtaining their consent, the sex and age of the children were recorded. The day before the first survey, children were issued with a small plastic container and they were asked to return the containers with a small portion of their morning stools. After stool collection, children were issued with a new container for stool collection of the next day. This procedure was repeated over five consecutive days. Further details of the study area and the children surveyed are provided elsewhere (UTZINGER *et al.*, 1998).

Stool specimen analysis

The stool specimens were brought to the central laboratory in Man, the region's main town. First, they were analysed macroscopically by recording the consistency, placing special emphasis on liquid specimens. Second, a single 42 mg Kato-Katz thick smear was processed from each stool specimen according to KATZ *et al.* (1972). Within 30 to 150 minutes the slides were examined quantitatively under light microscopy by one of four experienced technicians. The total number of eggs of *S. mansoni*, hookworms, *A. lumbricoides* and *T. trichiura* was counted. This procedure with a varying clearing time resulted in some variability in sensitivity for hookworm detection since eggs are destroyed rapidly on the slide. As a quality control measure 10% of the slides were randomly selected and re-examined the following day for the presence of *S. mansoni*, *A. lumbricoides* and *T. trichiura* eggs.

On day 3, an additional 1-2 gram portion of stool was collected and preserved in sodium acetate-acetic acid-formalin (SAF). The specimens were forwarded to a reference laboratory in Switzerland, processed according to MARTI & ESCHER (1990) and examined under light microscopy within two months. Helminth eggs that were counted included *S. mansoni*, hookworms, *A. lumbricoides* and *T. trichiura*. The presence of *E. histolytica/E. dispar* and *G. lamblia*, was assessed semi-quantitatively by distinguishing between five levels: 1+: 1-2 parasites per stool sample analysed, 3+: 1-2 parasites per microscopic field, 5+: more than 10 parasites per microscopic field. Categories 2+ and 4+ were in between. The presence of intestinal protozoa, such as *Entamoeba hartmanni*, *Entamoeba coli*, *Endolimax nana*, *Iodamoeba bütschlii*, *Chilomastix mesnili* and *Blastocystis hominis*, was also recorded.

Recent recommendations proposed that 'true' infection prevalence of *S. mansoni* should be expressed by the cumulative infection prevalence derived from readings of several repeated Kato-Katz thick smears from stool specimens collected over consecutive days (DE VLAS & GRYSEELS, 1992; DE VLAS *et al.*, 1992). In the present study, the cumulative results of the 4 repeated Kato-Katz readings combined with the single SAF analysis were used as 'gold standard' of infection for *S. mansoni*, hookworm, *A. lumbricoides* and *T. trichiura*.

Reported signs and symptoms and treatment of infected children

In a first phase, six focus group discussions (FGD) with groups of 8 schoolchildren were conducted according to DAWSON *et al.* (1992) to assess the perception of different intestinal signs and symptoms. The FGDs were hold as mixed groups and in French (the official school language in Côte d'Ivoire) with brief parts in Yacouba or Dioula (the main local languages). Following these FGDs a list of the six most common intestinal signs and symptoms was constituted: diarrhoea, blood in stool, worms in the faeces, 'running stomach' ('ventre qui coule'), 'turning stomach' ('ventre qui tourne') and 'itching stomach' ('ventre qui gratte').

In a second phase, the head teachers interviewed all the children with a brief structured questionnaire based on the FGD findings. They asked the children individually whether they had experienced one of the above signs and symptoms during the last month. At the end of the interviews, all *S. mansoni* infected children were treated with a single oral dose of praziquantel at the recommended standard dose of 40 mg per kg body weight (WHO, 1993). Infections with other helminths were treated six weeks later, using two oral doses of pyrantel (10 mg per kg body weight) given within 2 weeks.

Statistics

For data analysis only those children who had (1) at least four samples examined by Kato-Katz, (2) a SAF examination on day 3, and (3) completed the questionnaire were considered. The parasitological and interview data were double entered and cross-checked using the EpiInfo software (version 6.04; Centres for Disease Control and Prevention, Atlanta, Georgia, USA).

Univariate statistics using the Kruskal-Wallis test were performed to assess the effect of infection status by *E. histolytica/E. dispar*, *G. lamblia*, hookworm and *A. lumbricoides* with regard to age, sex and village. Logistic regression modelling techniques using the LOGISTIC software (DALLAL, 1988) were applied to assess the associations between (1) the intestinal parasites and (2) these parasites and the different intestinal signs and symptoms that were considered. For the four parasites of interest, baseline models were established, defining infected children as cases and incorporating the variables village, sex, age, all the other intestinal parasites and all reported signs and symptoms. A backward elimination technique was applied to remove the non-significant associations. The adjusted odds ratio (including 95% confidence intervals), the likelihood ratio and the p-values were computed for the associations that remained significant.

Finally, the diagnostic performance of the most promising signs and symptoms was assessed by calculating the sensitivity, specificity and predictive values.

9.4   Results

Univariate statistics

At least four Kato-Katz thick smear readings, complete results for the SAF examination on day 3 and responses to all questions were obtained from 209 children (87% of enrolled children). The median age was 12 years with a range between 8 and 16 years. There were statistically significantly more boys (135) than girls (74) (χ^2, 1 degree of freedom (d.f.) = 9.4, p = 0.002), and this unbalance was more pronounced with increasing age.

The day-to-day variation and the cumulative results of the different helminth infections derived from the four repeated Kato-Katz readings have been presented in detail elsewhere (UTZINGER *et al.*, 1998). Briefly, *S. mansoni* was the predominant helminth with a cumulative infection prevalence of 92.3%. It was followed by hookworms and *A. lumbricoides* with cumulative prevalences of 60.8% and 38.3%, respectively. Only 4 children were infected by *T. trichiura* (Table 9.1). The infection prevalences derived from the single SAF-conserved stool specimen were all lower than those resulting from the cumulative Kato-Katz readings. For *S. mansoni* and *A. lumbricoides* the SAF results considerably underestimated the cumulative infection prevalence; for hookworms, however, there was a good agreement. Combining the results of the single SAF examination with those of the 4 repeated Kato-Katz readings revealed the following: the additional SAF reading detected no additional *A. lumbricoides* infection but one additional *T. trichiura*, three additional *S. mansoni* and 19 additional hookworm infections (thus resulting in a cumulative hookworm infection prevalence of 70.8%; Table 9.1). These combined results were defined as 'gold standard' of helminth infections and were used in subsequent analysis.

The point prevalences of all intestinal protozoa infections are also presented in Table 9.1. The predominant species was *Entamoeba coli* with an infection prevalence rate of 66.5%. Other frequently observed protozoa were *Blastocystis hominis* and *E. histolytica/E. dispar* with point prevalence rates of 39.2% and 37.3%. The prevalence rate of *G. lamblia* was 12.0%.

As the main focus of the present paper is on *E. histolytica/E. dispar*, *G. lamblia*, hookworm and *A. lumbricoides* more detailed analysis was performed on these intestinal parasites.

Univariate statistics revealed that there was no significant association between an infection with *E. histolytica/E. dispar* and sex (Kruskal-Wallis H, 1 d.f. = 2.81, p = 0.094), age (H, 8 d.f. = 8.24, p = 0.410) and village (H, 2 d.f = 0.78, p = 0.678). The majority of *E. histolytica/E. dispar* infected children showed a level of infection of 2+ (46%) and 3+ (24%).

Infections with *G. lamblia* were also independent of sex (H, 1 d.f. = 0.91, p = 0.339), age (H, 8 d.f. = 4.25, p = 0.834) and village (H, 2 d.f = 1.20, p = 0.549). Fifty percent of the children who were infected with *G. lamblia* had an infection level of 2+.

Table 9.1

Overall results of infections with intestinal parasites among 209 schoolchildren screened on four consecutive days with Kato-Katz thick smears and on one day with an additional SAF – formol-ether concentration method.

Intestinal parasite (method, examination)	# positive	Prevalence (95% CI)
Helminths (Kato-Katz thick smears, 4 readings)		
Schistosoma mansoni	193	92.3 (87.9 – 95.6)
Hookworm	127	60.8 (53.8 – 67.4)
Ascaris lumbricoides	80	38.3 (31.7 – 45.2)
Trichuris trichiura	4	1.9 (0.5 – 4.8)
Helminths (SAF, on day 3)		
Schistosoma mansoni	114	54.5 (47.5 – 61.4)
Hookworm	111	53.1 (46.1 – 60.0)
Ascaris lumbricoides	13	6.2 (3.4 – 10.4)
Trichuris trichiura	2	1.0 (0.1 – 3.4)
Helminths (4 Kato-Katz thick smears & 1 SAF)		
Schistosoma mansoni	196	93.8 (89.6 – 96.6)
Hookworm	148	70.8 (64.1 – 76.9)
Ascaris lumbricoides	80	38.3 (31.7 – 45.2)
Trichuris trichiura	5	2.4 (0.0 – 2.6)
Protozoa (SAF, 1 day)		
Entamoeba coli	139	66.5 (59.7 – 72.9)
Blastocystis hominis	82	39.2 (32.6 – 46.2)
Entamoeba histolytica/E. dispar	78	37.3 (30.7 – 44.3)
Entamoeba hartmanni	60	28.7 (22.7 – 35.4)
Endolimax nana	52	24.9 (19.2 – 31.3)
Iodamoeba bütschlii	39	18.7 (13.6 – 24.6)
Chilomastix mesnili	28	13.4 (9.1 – 18.8)
Giardia lamblia	25	12.0 (7.9 – 17.1)

Hookworm infections were statistically significantly more often found in boys (H, 1 d.f. = 18.09, p < 0.001) and older children were more likely to be infected with hookworms (H, 8 d.f. = 23.00, p = 0.003). The association between a hookworm infection and village showed borderline significance (H, 2 d.f = 5.81, p = 0.055). Infections with *A. lumbricoides* were independent of sex (H, 1 d.f = 0.48, p = 0.490), age (H, 8 d.f = 4.23, p = 0.836) and village (H, 2 d.f = 4.94, p = 0.085).

Association with other intestinal parasites

Multiple intestinal parasite infections were very common in the study area, as shown in Figure 9.1. Interestingly, boys had a higher multiplicity of parasites than girls, while children aged 13-16 years had a higher multiplicity of parasites than younger children (aged 8-12 years).
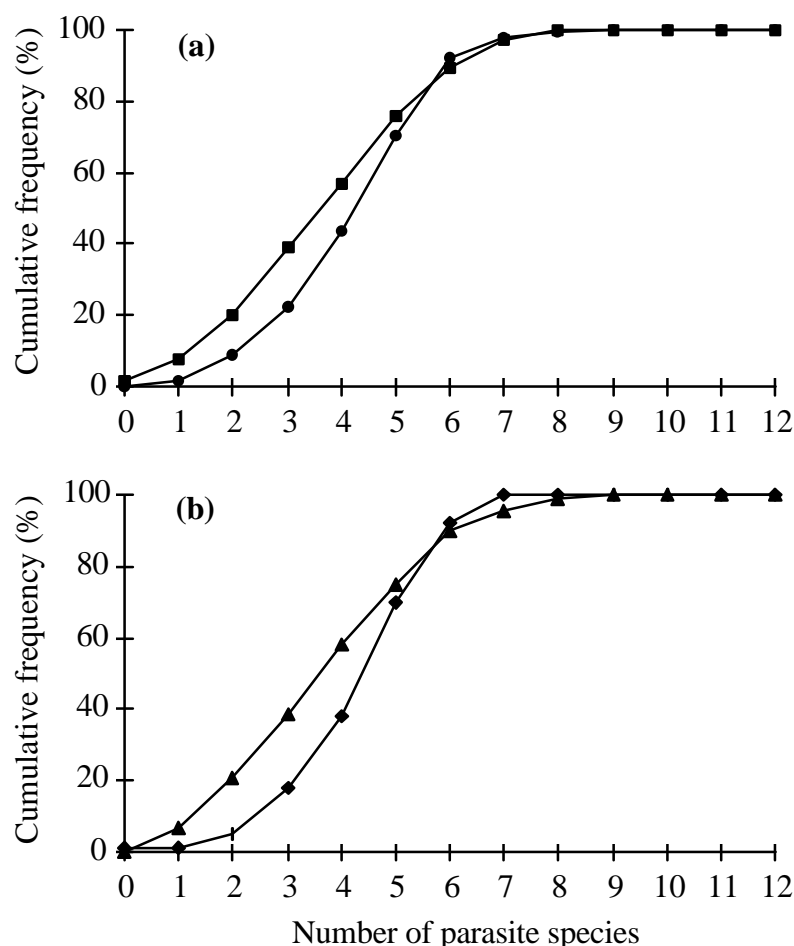
Figure 9.1

Cumulative frequency of multiparasitism among boys (points) and girls (squares) and stratified in two age groups (8-12 years: triangels, 13-16 years; dimonds) among 209 schoolchildren in western Côte d'Ivoire.

Multivariate statistics of relations between the intestinal parasites

The logistic regression analysis for investigating the relationship between an infection with *E. histolytica/E. dispar* and other intestinal parasites is presented in Table 9.2. It revealed that only infections with *Entamoeba coli* were associated with an *E. histolytica/E. dispar* infection (adjusted odds ratio (OR) = 2.44, 95% confidence interval (CI): 1.28-4.67, p = 0.005). An infection with *G. lamblia* showed no significant association with any other intestinal parasite (Table 9.2).

Further logistic regression analysis revealed that there was no significant association between a hookworm infection and any other intestinal parasite. The significant associations that were found in the univariate analysis between a hookworm infection and both sex and age also remained in the logistic regression (Table 9.2). However, the borderline significance between a hookworm infection and village did not appear in the logistic regression analysis (Table 9.2). An infection with *A. lumbricoides* showed no significant association with any other intestinal parasite. However, the logistic regression analysis revealed a significant association between an *A. lumbricoides* infection and village (adjusted OR = 1.58, 95% CI: 1.05-2.37, p = 0.026; Table 9.2).

Table 9.2

Logistic regression analysis for *Entamoeba histolytica/E. dispar*, *Giardia lamblia*, hookworm and *Ascaris lumbricoides*, being defined as 'case' to assess significant associations with other parasites and reported signs and symptoms.

Parasite	Association	Adjusted Odds ratio (95% CI)	Likelihood ratio statistics (1 d.f.)	p-value
E. histolytica/E. dispar	*Entamoeba coli*	2.44 (1.28-4.67)	7.78	0.005
	'Diarrhoea'	2.19 (1.09-4.40)	4.81	0.028
G. lamblia	'Turning stomach'	0.42 (0.17-1.06)	3.63	0.057
Hookworm	Sex	3.13 (1.64-6.25)	11.98	< 0.001
	Age	1.56 (1.23-1.97)	14.66	< 0.001
A. lumbricoides	Village	1.58 (1.05-2.37)	4.93	0.026

Stool consistency

The macroscopical stool inspection on day 3 recorded a total of 21 liquid/unformed specimens (10%). The cumulative number of children with at least one liquid stool specimen over four consecutive days was 52 (25%). There was no significant association between observed liquid stool specimens and an infection with *E. histolytica/E. dispar* and/or *G. lamblia*. Furthermore, no significant association was found between reported diarrhoea over the last month and observed liquid stool specimens.

Reported signs and symptoms

Only one significant association between intestinal parasite infections and reported signs and symptoms was found in our analysis. Children infected with *E. histolytica/E. dispar* reported significantly more often having had diarrhoea during the last month when compared with those non infected (adjusted OR = 2.19, 95% CI: 1.09-4.40, p = 0.028; Table 9.2).

The diagnostic performance of reported diarrhoea as a predictor for an infection with *E. histolytica/E. dispar* is characterised by a low sensitivity: 28.2% (95% CI: 18-9-39.7%), a

high specificity: 84.7% (95% CI: 77.2-90.2%), a moderate positive predictive value: 52.4% (95% CI: 36.6-67.7) and a moderate negative predictive value: 66.5% (95% CI: 58.7-73.5).

It was interesting to note that children who were infected with *G. lamblia* reported less often having had a 'turning stomach' during the last month (adjusted OR = 0.42, 95% CI: 0.17-1.06, p = 0.057; Table 9.2). This finding is difficult to interpret and might be due to chance.

9.5 Discussion

The high endemicity of intestinal amoebiasis and giardiasis was confirmed in the present study with schoolchildren from western Côte d'Ivoire, who showed point prevalences derived from a single SAF examination of 37.3% and 12.0%, respectively. It is likely that the true infection prevalence of these two intestinal protozoa are even higher, as single stool examinations fail to identify all infections, especially the light ones. In a previous study, examinations of multiple stool samples and the use of a mathematical model revealed that the probability of correctly identifying an infection with *E. histolytica/E. dispar* and *G. lamblia* was 61% and 75%, respectively (MARTI & KOELLA, 1993).

Hookworm was the most prevalent geohelminth. The cumulative infection prevalence after 4 repeated Kato-Katz readings and a single SAF examination was 70.8%. The second most frequently observed geohelminth was *A. lumbricoides*, with a cumulative infection prevalence of 38.3%. The day-to-day variation in the egg output of hookworms and *A. lumbricoides* was considerable, hence a single Kato-Katz reading would have resulted in a substantial underestimation of the "true" infection prevalences. Recommendations that the infection prevalence of *S. mansoni* should be assessed by repeated Kato-Katz readings (DE VLAS *et al.*, 1992; DE VLAS & GRYSEELS, 1992) seem therefore to be also relevant for geohelminths. Care is needed in assessing the infection prevalence of hookworms for which Kato-Katz thick smears are not ideal because the eggs tend to get overcleared rapidly by the glycerol in the stain. It is likely that the rather long and varying clearing time in our study (30 to 150 minutes) has led to some variation in the sensitivity of hookworm detection. This is the likely explanation for the fact that the single SAF examination was able to identify an additional 10% hookworm infections, while this was not the case for the other geohelminths.

Diagnosis of protozoa was made by light microscopy which has the disadvantage that it fails to distinguish between the cysts of *E. histolytica* and *E. dispar* (DIAMOND & CLARK, 1993) and such infections must therefore be reported as *E. histolytica*/*E. dispar*. New and more sophisticated techniques – such as the polymerase chain reaction technique, isoenzyme analysis and antigen detection – are necessary for the specific identification (GONZÀLEZ-RUIZ & WRIGHT, 1998). Unfortunately, such diagnostic techniques are not yet available for routine use in developing countries and appropriate methods are urgently needed (WHO, 1997).

This limitation represents a serious issue in our study since *E. histolytica* is thought to be responsible for nearly all the reported morbidity (CLARK, 1998) and since *E. dispar* is the more frequent infection with for example a ratio of 10:1 in South Africa (GATHIRAM & JACKSON, 1985). Consequently our assessment of the diagnostic performance of reported signs and symptoms is based on a substantial mis-classification on the infection side and this might explain the low sensitivity of reported diarrhoea in our findings.

Despite this limitation, reported diarrhoea was found to be significantly associated with *E. histolytica/E. dispar* infections. This confirms previous reports by other epidemiological studies that *E. histolytica/E. dispar* was associated with acute or chronic episodes of diarrhoea (CHATTERJEE *et al.*, 1989; SHETTY *et al.*, 1990; YOUNES, 1996). A further case-control study revealed that an infection with *E. histolytica/E. dispar* is statistically significantly more often reported in patients with diarrhoea than in controls (HENRY *et al.*, 1995).

Our diagnostic work was preceded by a careful qualitative analysis aimed at identifying the most commonly perceived intestinal signs and symptoms in the study children. Although we might have failed to identify some perceived signs or symptoms, especially the ones that do not have equivalents in the biomedical understanding of disease, it is likely that the list that we produced was a good basis for this work. As a result, it is rather unlikely that we missed a sign or symptom that might be equally good as diarrhoea for predicting infections with *E. histolytica/E. dispar*.

These observations raise some hope that perceived/reported diarrhoea may be of use in the rapid identification for *E. histolytica/E. dispar* infections, at least for the population studied. A potential confounding effect can be expected in areas with high levels of *S. mansoni* infections, since infected individuals report diarrhoea more often compared with non-infected individuals (GRYSEELS, 1992). In our own work in the same area we found an odds ratio of 1.7 (95% CI: 0.8-3.6) for this association (UTZINGER *et al*. 1998).

In summary, reported diarrhoea was the only useful symptom for the identification of *E. histolytica*/*E. dispar* infections in our population surveyed, while no useful sign or symptom was found for the other intestinal parasites. The specificity of this symptom was relatively high (85%) but its sensitivity was low (28%) which led to only moderate predictive values. The low sensitivity was probably a consequence of our inability to distinguish between pathogenic *E. histolytica* and non-pathogenic *E. dispar* infections. It is therefore recommended to further investigate the relationship between reported diarrhoea and specific *E. histolytica* infections with adequate diagnostic techniques in several places. Such investigations may conclude that reported diarrhoea is a reliable symptom for the rapid and low-cost identification of communities at a high risk of the pathogenic *E. histolytica* infections.

9.6 Acknowledgements

9.7 References

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10 Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial

Jürg Utzinger (PhD) [1,2], Eliézer K. N'Goran (PhD) [2,3], Amani N'Dri (MD) [4], Christian Lengeler (PhD, MSc) [1], Xiao Shuhua (MD) [1,5], Marcel Tanner (PhD, MPH) [1]

1   Swiss Tropical Institute, P.O. Box, CH–4002 Basel, Switzerland

2   Centre Suisse de Recherches Scientifiques, 01 BP 1303, Abidjan 01, Côte d'Ivoire

3   UFR Biosciences, Université de Cocody, 22 BP 582, Abidjan 22, Côte d'Ivoire

4   Grandes Endémies de Man, BP 470, Man, Côte d'Ivoire

5   Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, Shanghai 200025, China

Correspondence to: Prof Marcel Tanner, Swiss Tropical Institute, P.O. Box, CH–4002 Basel, Switzerland

Tel   +41 61 284 8283
Fax   +41 61 271 7951
e-mail   marcel.tanner@unibas.ch

10.1   Summary

Background – Chemotherapy with praziquantel is the current strategy of choice to control schistosomiasis. However, in view of concern about praziquantel tolerance or resistance, new drugs are needed. Artemether, a derivative of the antimalarial drug artemisinin, kills immature schistosomes of *Schistosoma japonicum*, and reduces the incidence of infections in field trials. Laboratory studies also showed activity by this drug against *S. mansoni*. We report a randomised double-blind placebo-controlled clinical trial of artemether to prevent *S. mansoni* infection.

Methods – The trial was done in an area of western Côte d'Ivoire endemic for *S. mansoni*. 354 schoolchildren were enrolled. Stool specimens were screened over four consecutive days, followed by two mass treatments with praziquantel 4 weeks apart. All *S. mansoni* negative children were randomly assigned to placebo (n=151) or artemether 6 mg/kg (n=138) orally six times once every three weeks. Adverse events were assessed 24 h after treatment. Perceived illness episodes were recorded once a week by interviewing the children using a standardised questionnaire. 3 weeks after the final medication *S. mansoni* infections were assessed by screening stool samples. Blood samples were examined for *Plasmodium falciparum* before the first and after the last artemether treatment.

Findings – Oral artemether showed no adverse reactions. The group that received artemether had a significantly lower incidence of *S. mansoni* infection (31/128 versus 68/140, relative risk: 0.50 (95% CI: 0.35-0.71), p=0.00006). The geometric mean egg output among positive children in the artemether group was significantly lower than in placebo recipients (19 versus 32 eggs/g stool, p=0.017). There was also a significant reduction in the prevalence of *P. falciparum*.

Interpretation – Oral artemether is safe and shows a prophylactic effect against *S. mansoni*. The use of artemether may be recommended in appropriated situations as an additional tool for more effective schistosomiasis control measures. However, the application needs to be carefully assessed especially in view of the concern that it could select for resistant plasmodia.

Key words: Artemether – Chemoprophylaxis – Côte d'Ivoire – *Schistosoma mansoni* – Schistosomiasis

10.2   Introduction

Among the parasitic diseases schistosomiasis is ranked second to malaria in terms of socioeconomic and public health importance (1, 2). The global strategy for controlling schistosomiasis is to reduce morbidity. No vaccine is available (3, 4), so chemotherapy currently has the key role in morbidity control (2). Praziquantel is the drug of choice – it is active against all schistosome species, can be easily administered, has high cure and egg reduction rates, and no or only mild side-effects (5, 6). However, field studies in a community in Senegal exposed to a very intense focus of *Schistosoma mansoni* showed unexpectable low cure rates after praziquantel (7, 8, 9). In mice, the possibility of selecting schistosomes largely insensitive to praziquantel has been shown after the administration of several subcurative doses of praziquantel (10). These observations raised concern about praziquantel tolerance or resistance. Oxamniquine (for *S. mansoni*) and metrifonate (for *S. haematobium*) are effective but are difficult to obtain in some African countries (11). The production of oxamniquine has been reduced and metrifonate has been withdrawn from the market (12).

Rapid re-infection limits the success of schistosomiasis control programmes (13), which has led to a call for additional control measures, and the idea of chemoprophylaxis as a treatment has gained in importance. For schistosomiasis, a drug that kills immature worms can be defined as chemoprophylaxis, because it prevents the development of the mature female worms which cause damage to the human host as a result of egg secretion (14). In laboratory experiments, Bout and collaborators identified cyclosporin A with very long-lasting prophylactic properties of up to 100 days (15). Derivatives of artemisinin (the Chinese drug *qinghaosu*), were tested in the laboratory and showed highest activity against immature worms (14).

Artemether is an artemisinin derivative that is already being widely and effectively used against malaria (16) and has no or only few side-effects (17). In *S. japonicum* animal models, artemether given once every 2 weeks showed high worm reduction rates of 89-94% (18, 19). The prophylactic effect of artemether was also confirmed in seven randomised double-blind placebo-controlled trials in China with more than 4500 individuals exposed to *S. japonicum* in areas of low endemicity and low re-infection rates. Artemether, given once every two weeks at a dose of 6 mg/kg for a total of 2-10 doses (covering half or the entire transmission period) was well tolerated and reduced the incidence and intensity of infection significantly (14).

For *S. mansoni*, the killing of immature worms by artemether was shown in vitro (20), and is well documented in mice with worm reduction rates of 97-100% (21). The highest efficacy was seen between days 7 and 28 after the mice had been infected. This is the period when praziquantel and other schistosomicides are less effective (22).

In view of these findings, we organised a first randomised, double-blind, placebo-controlled trial to assess the preventive effect of oral artemether against *S. mansoni* infection in an area with a high prevalence and high re-infection rate in Côte d'Ivoire.

10.3 Methods

Area and population

The trial was done between November, 1998, and July, 1999, in the village of Fagnampleu, in the region of Man in western Côte d'Ivoire. This village, with a population of about 2000, lies on a tarmac road 20 km east of Man, the region's main tow. There are two distinct seasons, with rains between April and September; and the mean annual rainfall is 1600 mm (23).

The Man region is a highly endemic focus of *S. mansoni* (1) with an infection prevalence of 54% among schoolchildren (24). There has been no schistosomiasis control campaign in this area so far. At the beginning of 1998, screening of stool samples from 91 schoolchildren attending standards 4-6 in Fagnampleu showed a prevalence of *S. mansoni* infection of 86%. A study in a neighbouring village showed that re-infection rates are high during the main transmission period between November and June-July (23). Malaria is also endemic, but no solid data existed for Fagnampleu before the start of our work.

Study design

The study was a randomised double-blind placebo-controlled trial to assess the prophylactic effect of oral artemether to prevent *S. mansoni* infection among schoolchildren. The primary outcome measures were the incidence of *S. mansoni* infection and the geometric mean egg output of positive children. A sample size of 252 children receiving either artemether or a placebo was estimated to give the study at least 90% power at a 5% significance level to detect a 50% difference in the incidence rate of *S. mansoni* infections between the two groups. This calculation assumed that 50% of the children in the placebo group would be re-infected with *S. mansoni* within 5 months during the main transmission season (23).

The trial was approved by the Institutional Review Board of the Swiss Tropical Institute and received ethical clearance from the Ministry of Public Health of Côte d'Ivoire. The study objectives were explained in detail to the chief and authorities of the village, and the school director. After they had given their consent, a meeting was organised in the village with the children's parents and/or caretakers. Detailed information was provided about the aims, procedures and potential risks of the study. After obtaining consent, head teachers prepared class lists with the name, sex and age of the schoolchildren. At the beginning of the trial, the study physician carried out a full clinical examination of all children from standards 1-6, including assessment of liver- and spleen enlargement and anaemia. All children seemed healthy and had no apparent chronic or debilitating conditions; therefore they were eligible for study enrolment.

At enrolment, all schoolchildren were issued with a transparent plastic container (volume 125 ml), and invited to return the containers the following day with a small portion of their morning stool. This procedure was repeated over four consecutive days. The day after the last stool collection, all children received a treatment of praziquantel in two doses of 30 mg/kg a

few hours apart. A second praziquantel mass treatment (40 mg/kg) was administered four weeks later after stool specimens had again been collected over four consecutive days. Those children who had at least three stool specimens analysed at both surveys were eligible for randomisation. Finally, stool specimens were collected again four weeks later, and all schoolchildren provided a finger-prick blood sample for thick and thin blood films for malaria parasite examination (Figure 10.1).

Indistinguishable looking capsules of artemether (40 mg) and a placebo (starch) were provided by the Kunming Pharmaceutical Corp., Kunming, China. The product specification and sterility were confirmed in laboratory tests (bacteria, mycoses and *Bacillus coli*) and then packed in 26 tins identified only by number, each containing 500 capsules (13 tins artemether, 13 placebo). Schoolchildren were stratified by school year and randomised to a tin (i.e. in blocks of 26) by an independent statistician who was not otherwise involved in the trial.
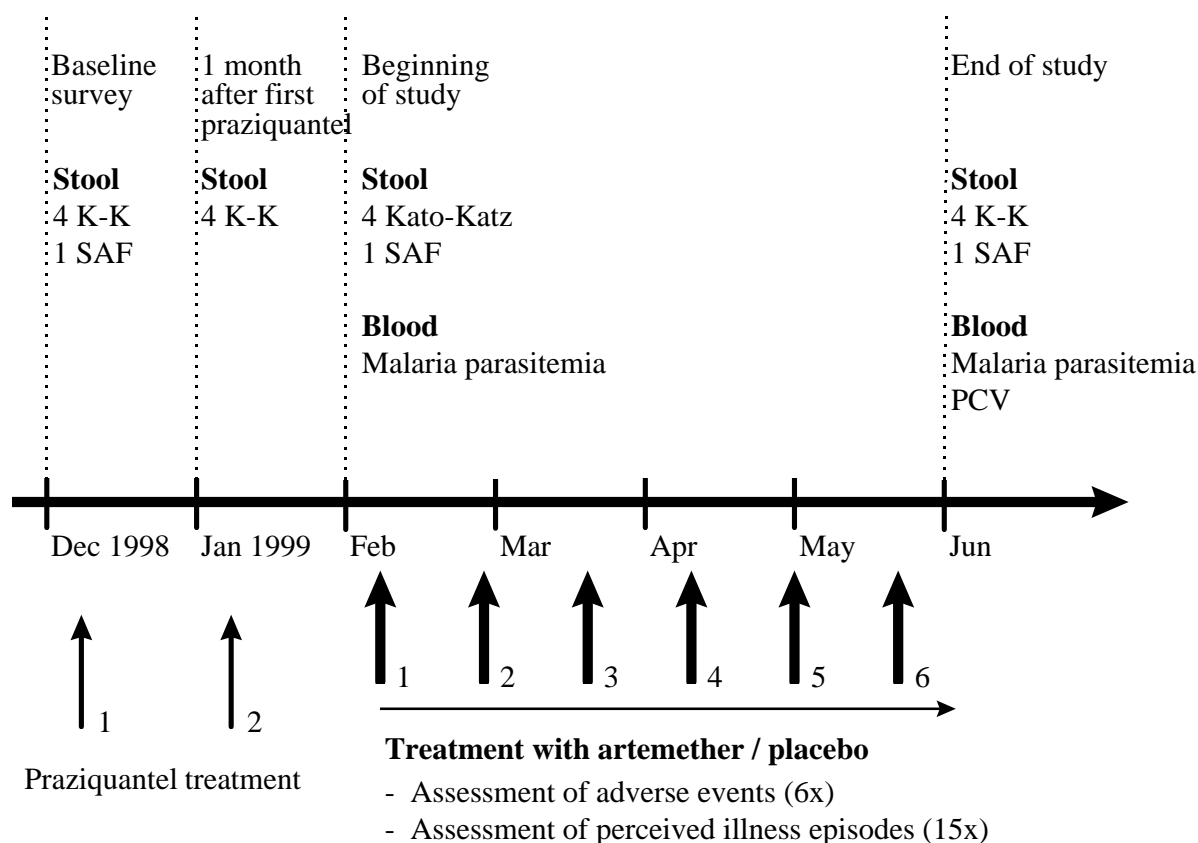

Figure 10.1
Study design

The first dose of artemether (6 mg/kg) or placebo was administered by the study physician in the afternoon of the last stool examination. Treatment at the same dose was repeated every three weeks for a total of 6 times. After each dose, children remained under medical surveillance for at least 1 hour. Adverse events within 24 hours after artemether administration were assessed by the physician, who interviewed children on the day after each dose had been given, using a standard questionnaire. Those children who reported adverse events were carefully examined by the study physician and when necessary, action was taken according to standard procedures of primary health care facilities in Côte d'Ivoire.

Perceived illness episodes during the previous week were assessed using a questionnaire administered by the teacher. This was done throughout the trial, starting on day 7 after the first dose, for a total of 17 weeks (omitting weeks 6 and 7, when the school was on holiday). A weekly visit to the school was carried out by the physician to monitor the accuracy of the teacher's interviews, to provide medical treatment, or, if necessary, to refer children to the central hospital in Man. In addition, he reviewed all absences from school and assessed their reasons.

Three weeks after the last treatment, a final parasitological survey was carried out. Stool specimens were collected over four consecutive days, and finger-pricks were done to prepare thin and thick blood smears and to collect blood in heparinised microcapillary tubes for later measurement of the packed cell volume (PCV) (Figure 10.1).

Laboratory procedures

Procedures were designed to examine *S. mansoni* and also other intestinal infections which could be present concurrently, as well as malaria. Stool specimens were brought to the central laboratory in Man, and a single 42-mg Kato-Katz thick smear was processed from each specimen according to a standard method (25). The slides were allowed to clear for at least 45 min and were examined within 1 hour under a light microscope (Wild Heerbrugg, Switzerland) at 100x magnification by 1 of 5 experienced microscopists. The total number of eggs of *S. mansoni*, and also of hookworms, *Trichuris trichiura* and *Ascaris lumbricoides*, was counted. For quality control, the senior microscopist re-examined a random sample of 10% of the slides the following day.

In three of the surveys (Figure 10.1) a 1-2 g portion of each stool specimen was also preserved in sodium acetate-acetic acid-formalin (SAF) and processed according to Marti & Escher (26). These were examined under light microscope by x50 oil immersion lens and x10 eyepieces by 2 experienced microscopists for intestinal protozoa.

Thick and thin blood films were stained with Giemsa and read under a light microscope with a x50 oil immersion lens and x10 eyepieces. The species-specific densities of malaria parasites were analysed by counting the number of parasites per 200 white blood cells (WBC). When fewer than 10 parasites were found, the reading was continued up to 500 WBC. Parasite

numbers were converted to a count/µL by assuming a standard WBC count of 8000/µL. At the end of the study, the PCV was measured using a microhaematocrit centrifuge.

Data management and statistical analysis

All data were double-entered and verified using EpiInfo software (version 6.04; Centres for Disease Control and Prevention, Atlanta, Georgia, USA) and analyses were done with EpiInfo and STATA (version 6.0, Stata Corp., Collage Station, Texas, USA). The primary outcome measures were (i) the incidence of *S. mansoni* infection after four months of treatment and (ii) the geometric mean egg output of positive children. The final statistical analysis included all children who had been randomised, were *S. mansoni* negative after praziquantel treatments, received all 6 doses of artemether or a placebo, and provided at least 3 stool specimens at the end of the study.

For assessment of perceived adverse events, for each symptom (e.g. headache) the total number of positive reports in the 6 sets of interviews was calculated and expressed as a proportion of all interviews. Logistic models with random effects to account for individual heterogeneity were used, applying the maximum-likelihood approach, to calculate confidence intervals for these proportions and to test for the differences between the groups (27). Statistical significance was assessed using the likelihood ratio test. For assessment of perceived illness episodes, the total number of episodes of each type was divided by child-weeks, to give the relative rate for each group. A logistic model with random effects was again used to test the differences in rates. Comparison of concurrent infections between artemether and placebo recipients were tested by comparison of proportions, using a chi-square test.

10.4   Results

Screening and treatment

349 of the 354 children enrolled in the school provided at least three stool specimens at the baseline survey for Kato-Katz thick smears (Figure 10.2). 28 children were excluded: 15 missed the second treatment with praziquantel, and 13 provided fewer than three stool specimens before the first artemether treatment. 321 children were randomly assigned to the artemether (n=157) or placebo (n=164). 32 who remained *S. mansoni* positive (19 artemether, 13 placebo) and 5 who left the area and missed one or more of the treatments (2 artemether, 3 placebo) were excluded, and during the final parasitological screening, 16 children (8 artemether, 8 placebo) dropped out, because they provided fewer than three stool specimens. The final cohort analysed consisted of 128 children receiving artemether and 140 receiving the placebo.

Comparison of groups

The two groups were similar at the beginning of the study in terms of age and sex (Table 10.1). The prevalences of *S. mansoni* infection at baseline were 71.9% and 77.1% for the artemether and the placebo groups, respectively, and the geometric mean egg outputs of positive children were 88 epg (95% CI: 63-122 epg) and 106 epg (95% CI: 81-139 epg), respectively (Table 10.1). In addition to being similar in terms of prevalence and intensity of *S. mansoni* infection at baseline the two groups also showed similar cure and egg reduction rates after praziquantel treatment (Table 10.1). No difference was found for baseline prevalences of geohelminths, intestinal protozoa and malaria (Table 10.2).

Effects of artemether against S. mansoni

At the end of the study, i.e. 5 months after the second mass treatment with praziquantel and three weeks after the sixth dose of artemether or a placebo, a significant difference was seen in the rates of re-infection with *S. mansoni*: artemether: 31/128 versus placebo: 68/140 (relative risk: 0.50 (95% CI: 0.35-0.71), χ^2=16.0, p=0.00006, Table 10.1). There was also a significant reduction in the infection intensity in positive children, as expressed by their geometric mean egg output: artemether: 19 epg (95% CI: 13-26 epg) versus placebo: 32 epg (95% CI: 25-42 epg, t-test=2.42, p=0.017, Table 10.1).

Adverse events

No serious or severe adverse events due to oral artemether were recorded immediately after treatment and no child needed medical care. Compliance for reporting adverse events was excellent (1581/1608). No symptom was significantly more often reported by artemether recipients during the first 24 hours after treatment than by children given a placebo (Table 10.3).

Perceived illness episodes

Table 10.3 also summarises the reported illness episodes during the whole period of artemether treatment. Compliance was excellent (3971/4020). Children who had received artemether were significantly less likely to report headache.

Effect of artemether against other parasites

Artemether showed no effect against geohelminths and intestinal protozoa (Table 10.2). However, the group that received artemether had a significantly lower prevalence of *Plasmodium falciparum* at the end of the survey: 75/126 artemether versus 106/136 placebo (relative risk=0.76, 95% CI: 0.64-0.90, χ^2=9.54, p=0.002). Furthermore, the PCV in the artemether group was significantly higher than in the placebo group at the end of the survey: mean artemether=38.8 (SE)=0.3) versus mean placebo=37.9 (SE=0.3, t-test=2.28, p=0.023).
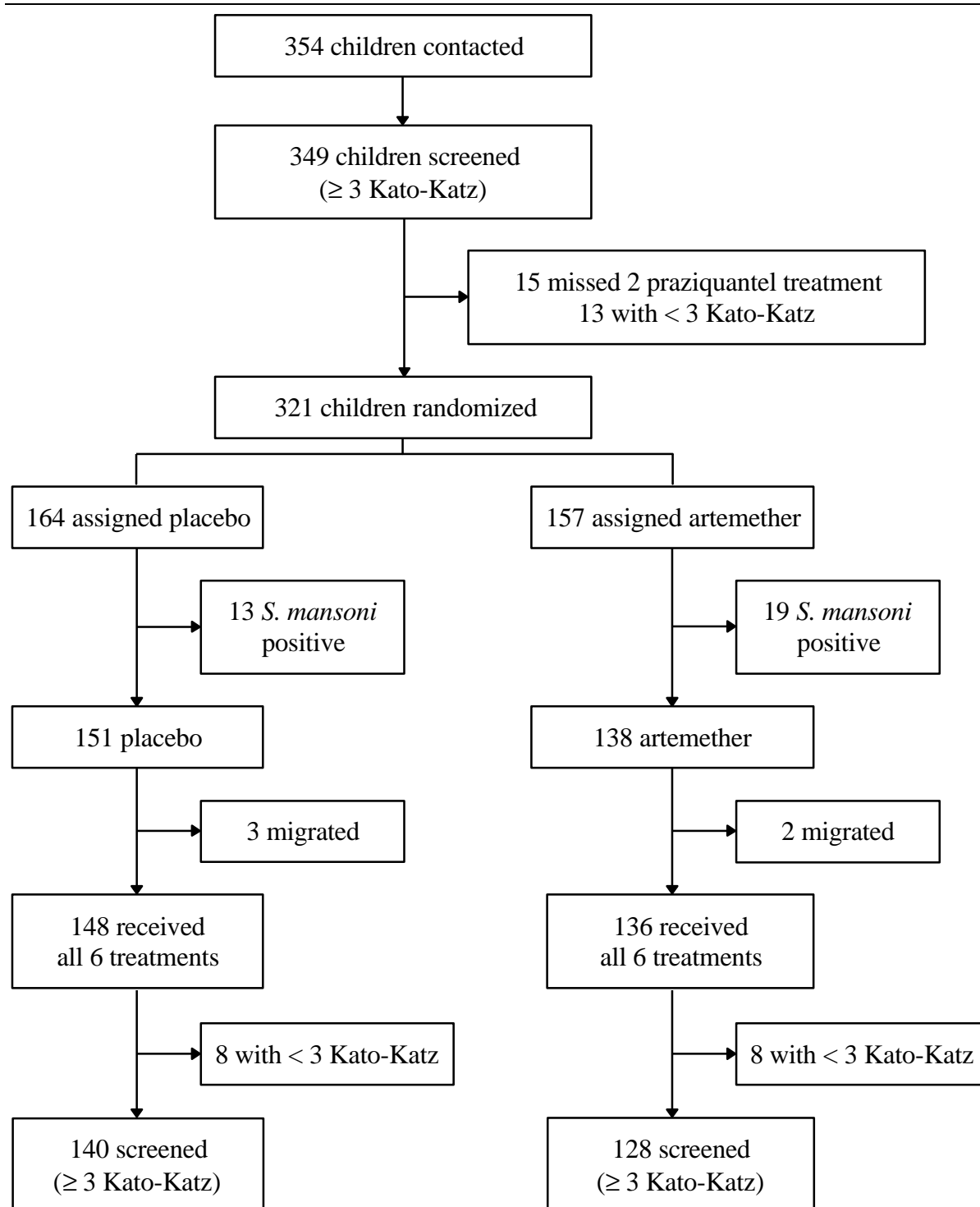
Figure 10.2
Trial profile

10.5   Discussion

The study showed that oral artemether is safe and has a clear prophylactic effect against *S. mansoni*. The incidence of *S. mansoni* infection was 50% lower in those children who received artemether rather than placebo. The intensity of infection among the positive children was also reduced significantly. These results are based on repeated stool analyses with at least three consecutive Kato-Katz smears. Our preceding work in the same area showed that such a procedure gives a reliable measure with a sensitivity above 95% (28). Our results confirm the prophylactic properties of artemether previously found in laboratory mice and hamsters infected with *S. mansoni* (21). The protective effect, calculated on the basis of a single smear was 74%. However, it is well established that repeated stool analyses are mandatory to detect "all" infections (29).

The protective effect of artemether was shown in an area highly endemic for *S. mansoni* with an infection prevalence at baseline of 75% and with a rapid re-infection rate of 48% within only 5 months, as evidenced in the placebo group. The community studied here perceived *S. mansoni* as one of the most severe health problems they faced. The village health worker invited our research team to work in this village, which allowed us to set up an excellent collaboration and could explain the high compliance rates. The reduction in the incidence of reinfection (50%), is slightly lower than the rates reported for *S. japonicum* in five clinical trials done in China (14). However, it is difficult to compare the Chinese studies with ours, because of the different schistosome species and, because in China endemicity and reinfection rates (9-27%) were lower and artemether was given once every second week.

Our results are encouraging and results from animal experiments indicate that the effect could be improved by modifying the procedure, by earlier administration of the first dose of artemether at week 2 or 3 after praziquantel treatment instead of week 4, and reduction of the treatment intervals to 2 instead of 3 weeks (21). It is interesting to note that in laboratory experiments and a subsequent field trial carried out in China, artesunate, which is another derivative of artemisinin, has also shown a prophylactic effect against *S. japonicum* (30). Therefore, it is likely that artesunate, as well as other artemisinin derivatives, will also have a prophylactic effect on *S. mansoni*.

The study design implied that data on possible concurrent infections other than *S. mansoni* could be generated. Although the effect of artemether on other intestinal parasites has not been studied in detail, our results indicated that at the dosage given (6 mg/kg) it had no effect. In the case of malaria, some effect was to be expected, since artemether is well known to be active against malaria. Although artemether was given only at six occasions with three weeks intervals, a significant reduction in the prevalence of *P. falciparum* was observed. This may explain why the group of children receiving artemether reported headaches less often. Finally, a significant increase in the PCV in artemether recipients was measured.

Preceding observations and our own findings show that it is of interest to actively pursue research and development of drugs that act against different stages of parasites. In the case of schistosomiasis, control measures could be improved and might even lead to higher cure rates by combination therapy with drugs with different mode of actions, one acting against immature worms, e.g. artemether, and the other against adult worms, e.g. praziquantel. Such an approach might also reduce the risk of developing resistance. Laboratory data has indicated the risk of selecting strains of parasites less sensitive to praziquantel, when the drug is given at an early time after infection, when schistosomes are known to be insensitive to the drug (10, 22).

While this trial showed a prophylactic effect of artemether against *S. mansoni* in humans, there are a number of important questions to be addressed and discussed before there is wider application. Derivatives of artemisinin are the most rapidly-acting of all antimalarial drugs at present in use, and are effective against severe malaria and multi-drug-resistant falciparum malaria (16, 17). Therefore a careful protection of the few remaining effective drugs against malaria is mandatory.

In view of recent attempts to establish a more appropriate design for malaria treatment, suggesting combination therapy including a derivative of artemisinin (31), it remains to be assessed to what extent this will affect schistosomiasis transmission and endemicity in different sites.

There are three potential applications of our findings. First, the use of artemether as an additional tool in the control of schistosomiasis, at present only in areas where there is no malaria, such as Brazil, Venezuela, and Egypt. Second, focal application of artemether for a limited time in remaining *S. mansoni* foci where transmission is low and control close to eradication, for example in Botswana. Third, as prophylaxis for workers who cannot avoid exposure (eg, canal cleaners in irrigation systems in Sudan), for travellers, and in emergency situations such as flood-relief work where many previously-unexposed people may be in contact with infected water, as was the case in China. Our findings should therefore stimulate the discussion on schistosomiasis control strategies and may help to tailor more effective measures for specific endemic settings.

Table 1

Effect of praziquantel and repeated artemether treatment on *Schistosoma mansoni* infection prevalence and intensity (n=140 in placebo group; n=128 in artemether group; for study design see Figure10.1).

	Baseline (December 1998)		One month after first praziquantel treatment (January 1999)		Beginning of study; one month after second praziquantel treatment (February 1999)		End of study (June 1999)	
	Placebo	Artemether	Placebo	Artemether	Placebo	Artemether	Placebo	Artemether
Age (years)								
6-8	61	59						
9-11	54	48						
12-15	25	21						
Sex								
Male	85 (60.7%)	68 (53.1%)						
Female	55 (39.3%)	60 (46.9%)						
***S. mansoni* infection level**								
Negative (0 epg)	32 (22.9%)	36 (28.1%)	110 (78.6%)	106 (82.8%)	140 (100%)	128 (100%)	72 (51.4%)	97 (75.8%)
Light infection (1-100 epg)	50 (35.7%)	48 (37.5%)	28 (20.0%)	21 (16.4%)	0 (0%)	0 (0%)	56 (40.0%)	29 (22.7%)
Moderate infection (101-400 epg)	39 (27.9%)	25 (19.5%)	2 (1.4%)	1 (0.8%)	0 (0%)	0 (0%)	12 (8.6%)	2 (1.6%)
Heavy infection (> 400 epg)	19 (13.6%)	19 (14.8%)	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0%)	0 (0.0%)	0 (0.0%)
All infections	**108(77.1%)**	**92(71.9%)**	**30(21.4%)**	**22(17.2%)**	**0 (0%)**	**0 (0%)**	**68 (48.6%)**	**31 (24.2%)***
Geometric mean intensity (95% CI) in epg †	**106 (81-139)**	**88 (63-122)**	**15 (10-21)**	**17 (11-26)**	**0**	**0**	**32 (25-42)**	**19 (13-26) ***

epg=egg per gram of stool; *p<0.05; †only positive children included.

Table 2

Number of positive, percentages and mean differences for all parasites assessed (except *S. mansoni*), at beginning and end of the study

	Beginning of artemether treatment (February 1999)			End of study (June 1999)		
	Placebo	Artemether	Difference in % (95% CI)	Placebo	Artemether	Difference in % (95% CI)
Geohelminths (≥ 3 Kato-Katz)						
Hookworm	51 (36.4%)	48 (37.5%)	-1.1 (-20.1-17.9)	82 (58.6%)	74 (57.8%)	0.8 (-14.7-16.3)
Trichuris trichiura	3 (2.1%)	2 (1.6%)	0.5 (-23.3-24.3)	8 (5.7%)	7 (5.5%)	0.2 (-23.1-23.5)
Ascaris lumbricoides	1 (0.7%)	1 (0.8%)	-0.1 NA	2 (1.4%)	1 (0.8%)	0.6 (-23.3-24.5)
Intestinal protozoa (1 SAF) [a]						
Entamoeba coli	95 (68.8%)	83 (65.9%)	2.9 (-10.9-16.7)	77 (56.6%)	82 (66.1%)	-9.5 (-24.6-5.6)
Endolimax nana	66 (47.8%)	57 (45.2%)	2.6 (-15.1-20.3)	49 (36.0%)	50 (40.3%)	-4.3 (-23.4-14.8)
Entamoeba hartmanni	28 (20.3%)	31 (24.6%)	-4.3 (-25.6-17.0)	23 (16.9%)	22 (17.7%)	-0.8 (-22.9-21.3)
Iodamoeba bütschlii	27 (19.6%)	17 (13.5%)	6.1 (-16.0-28.2)	24 (17.6%)	19 (15.3%)	2.3 (-19.9-24.5)
Chilomastix mesnili	20 (14.5%)	12 (9.5%)	5.0 (-17.7-27.7)	20 (14.7%)	14 (11.3%)	3.4 (-19.3-26.1)
Blastocystis hominis	17 (12.3%)	22 (17.5%)	-5.2 (-27.5-17.1)	11 (8.1%)	5 (4.0%)	4.1 (-19.5-27.7)
Giardia duodenalis	15 (10.9%)	7 (5.6%)	5.3 (-17.9-28.5)	7 (5.1%)	6 (4.8%)	0.3 (-23.3-23.9)
Entamoeaba histolytica/E. dispar	10 (7.2%)	5 (4.0%)	3.2 (-20.3-26.7)	13 (9.6%)	17 (13.7%)	-4.1 (-27.0-18.8)
Malariometric indices [b]						
Plasmodium malariae	4 (2.9%)	4 (3.1%)	-0.2 (-23.8-23.4)	3 (2.2%)	4 (3.2%)	-1.0 (-24.9-22.9)
Plasmodium falciparum	88 (63.3%)	86 (67.7%)	-4.4 (-18.5-9.7)	106 (77.9%)	75 (59.5%)	18.4 (4.8-32.0)*
Geometric mean density/μL (95% CI) †	614 (342-616)	459 (342-616)		673 (512-886)	911 (655-1267)	
Packed cell volume (SE) [c]	NM	NM		37.9 (0.3)	38.8 (0.3)	

CI=confidence interval; SE=standard error; NM=not measured; NA=not applicable; *p<0.05; †only positive children included.

a) Cohort: Begin of study (placebo: n=138; artemether: n=126); End of study (placebo: n=136; artemether: n=124)

b) Cohort: Begin of study (placebo: n=139; artemether: n=127); End of study (placebo: n=136; artemether: n=126)

c) Cohort: End of study (placebo: n=121; artemether: n=106)

Table 3

Adverse events due to artemether treatment after 24 hours and reported illness episodes

Indicator	Adverse events (after 24 hours) [a]				Reported illness episodes (child-weeks) [b]			
	Placebo	Artemether	Relative risk (95% CI)	p-value *	Placebo	Artemether	Relative rate (95% CI)	p-value *
Abdominal pain	30	25	0.90 (0.46-1.77)	0.769	180	133	0.77 (0.50-1.19)	0.234
Headache	15	27	2.10 (0.97-4.52)	0.056	195	130	0.60 (0.41-0.90)	0.012
Diarrhoea	6	0	0.00 --	NA	40	21	0.45 (0.20-0.99)	0.049
Vomiting	4	8	2.20 (0.66-7.34)	0.199	33	24	0.81 (0.45-1.44)	0.471
Fever	4	3	0.82 (0.18-3.67)	0.794	30	25	0.89 (0.47-1.68)	0.717
Cough	2	5	2.75 (0.53-14.20)	0.203	116	88	0.80 (0.50-1.27)	0.342
Dizziness	1	4	4.39 (0.49-39.40)	0.186	23	8	0.38 (0.16-0.94)	0.031
Blood in stool	0	0	-- --	NA	43	37	0.89 (0.42-1.90)	0.764

CI=confidence interval; NA=not applicable; *likelihood ratio test

a)   Denominators for adverse events: 826 observations for placebo and 755 observations for artemether group

b)   Surveillance periods for reported signs: 2077 child-weeks for placebo and 1894 child-weeks for artemether group

10.6   Contributors

Jürg Utzinger and Eliézer K. N'Goran contributed to the design, were responsible for the on-site execution and coordination, data analysis, and preparation of the paper. Amani N'Dri had all the clinical responsibility, contributed to the on-site execution and coordination, and assessed adverse events of oral artemether. Christian Lengeler contributed to the design, on-site execution, data analysis and writing of the paper. Xiao Shuhua was responsible for the rationale and design, assured the provision of the drugs used and contributed to the writing of the paper. Marcel Tanner was responsible for the rationale and design, data analysis, contributed to the paper writing and assured the coordination of the trial.

10.7   Acknowledgements

10.8   References

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11 Discussion and Conclusion

11.1 Schistosomiasis control and high risk groups

Human schistosomiasis is a chronic and debilitating disease and remains one of the most prevalent parasitic infections in tropical and subtropical environments (WHO 1999). Due to its chronic nature, the disease affects labour capacity, and this has a major negative impact on the socio-economic development of many endemic regions (Tanner 1989). Schistosomiasis is related to water sources, and in view of the increasing number of water resource schemes being developed, it is expected that the disease will gain in importance (Mott *et al*. 1995). The current global aim in controlling schistosomiasis is morbidity control with, chemotherapy playing the key role (WHO 1993, 1999). This was not always the case, and within a relatively short historical period schistosomiasis control has undergone two major conceptual changes. First, there was a shift from transmission control, concentrating on the intermediate snail host, to morbidity control. Second, there was a change from vertically-structured and centralised programmes to integration of control activities into the primary health care system (Mott 1984, 1987, Gryseels 1989, Tanner 1989, Pervilhac *et al.* 1998).

The advent of safe, single dose and effective antischistosomal drugs that showed high cure and egg-reduction rates (WHO 1985, King *et al*. 1989, Kumar & Gryseels 1994), and the availability of simple but reliable diagnostic techniques brought about the first conceptual change (WHO 1985, Gryseels 1989, Tanner 1989). For a time, the control, and in some particular areas even eradication, of schistosomiasis was believed to be a realistic perspective. Population-orientated chemotherapy was first proposed in the early 1980s (WHO 1983), and subsequently many programmes in endemic countries were launched, following this suggestion. Although the prevalence and intensity of schistosomiasis (Brinkmann *et al*. 1988, Savioli *et al*. 1989, Gryseels *et al*. 1991 Engels *et al*. 1993), as well as related morbidity (Schmidt-Ehry 1986, Gryseels & Polderman 1987, Polderman & De Caluwé 1989, Hatz *et al*. 1998) were reduced significantly, the initial success of these programmes failed to be sustained in the long term. Rapid re-infection was the major drawback and it was observed that when the programmes came to an end, both infection and intensity levels rapidly returned to pre-treatment levels (Polderman 1984, Wilkins 1987, Gryseels *et al*. 1991, Hatz *et al*. 1998). It became clear that the control of schistosomiasis requires a long-term commitment and should be integrated in health care facilities. Ideally it should make use of a multiplicity of control measures aiming also at transmission control (Mott 1987, WHO 1993).

Assessing local priorities prior to developing and implementing control activities, and encouraging active community participation, increases the likelihood that control efforts will be sustained (Tanner *et al*. 1986). This usually calls for a decentralised, district-based organisation within the primary health care system. However, there are particular situations that may still justify external and vertically-structured assistance for a limited time. One example are situations of rapid spread following ecological modifications, as in northern Senegal, where an

outbreak of *S. mansoni* occurred only two years after the completion of the Diama dam (Gryseels *et al*. 1994, Picquet *et al.* 1996, Southgate 1997). There are also situations where local authorities are unable to implement a control programme on their own, for example in situations of political unrest. This was the case in northern Cambodia in 1992, when an important focus of *S. mekongi* was rediscovered. Severe pathology was revealed during a household survey with 1,396 people examined. Hepatomegaly, splenomegaly, visible diverted circulation and ascites were observed in 48.7%, 26.8%, 7.2% and 0.1% of the participants, respectively. This community had a clear perception of the severity of the disease, causing an immense psychosocial impact. People were scared and they said they feared death, infirmity and invalidity (Biays *et al*. 1999, Stich *et al*. 1999).

There are two major features of the epidemiology of schistosomiasis that are of great importance for the development and implementation of control strategies. Firstly, the disease is focally distributed (Webbe & Jordan 1993, WHO 1993, Malone *et al*. 1997). This means that schistosomiasis may be highly prevalent in one village but virtually absent in a neighbouring village. Secondly, in places where schistosomiasis is endemic, there is a high aggregation of worms (and thus excreted eggs) within the human population, with only few individuals being responsible for a large part of the disease burden (Anderson & May 1985, Guyatt *et al*. 1995). It has been observed in many endemic areas that the local people have a clear perception of the disease and recognise common signs and symptoms, and often there are specific local terms for these. This is well documented for *S. haematobium* (Zumstein 1983, Mott *et al*. 1985, Tanner & de Savigny 1987, Savioli *et al*. 1989, Lengeler 1991a, b, c, 1992, Red Urine Study Group, 1995, N'Goran *et al*. 1998, Useh & Ejezie 1999, Mafe *et al*. 2000), for *S. mansoni* (Hailu *et al*. 1995, Red Urine Study Group 1995, Booth *et al*. 1998, Utzinger *et al*. 1998), for *S. japonicum* (Zhou *et al*. 1998) and also for *S. mekongi* (Biays *et al*. 1999, Stich *et al*. 1999). As a consequence, it is most likely that the local communities in such places give schistosomiasis a high priority.

Schistosomiasis control programmes can take advantage of the focal and aggregated nature of the disease, and also make use of the community's perception of the importance of the disease. Means of rapid assessment which are able to determine rapidly, inexpensively but accurately where the communities at highest risk of schistosomiasis are located, are therefore pivotal as a first stage in the development of a control programme (Vlassoff & Tanner 1992). Such an approach fosters the concentration of limited resources where they are most needed, thereby allocating them in a cost-effective way.

11.2 The use and wide-scale application of questionnaires for *S. haematobium* in Côte d'Ivoire

One decade ago, a rapid, inexpensive, two-step approach was developed in two rural districts in Tanzania which allowed schools with the highest levels of *S. haematobium* infections to be identified (Lengeler *et al*. 1991a, b, c, 1992). Since schistosomiasis is generally most prevalent in school-age children, data from schools will normally reflect the situation in the community as a whole. Subsequently, the technique was validated in seven other African countries, and with one exception, Ethiopia (Jemaneh *et al*. 1996), showed an excellent diagnostic accuracy in terms of safely excluding those communities where *S. haematobium* was not a problem (Red Urine Study Group 1995). The technique relies on the existing health and education services and involves the active participation of the teachers, who are interviewing children about commonly perceived symptoms and diseases experienced in the recent past. The method is fully integrated within the existing administrative structure at the district level, which is a key factor explaining the consistent success obtained so far. The committed participation of teachers, which is well reflected in the high return rates of completed questionnaires (75-100%), is an excellent example of the integration of this technique.

Based on the experiences of this "indirect questionnaire approach", simple guidelines for its use were drawn up by the World Health Organization (Chitsulo *et al*. 1995). The aim was to equip district health managers with this powerful tool, so that they could apply it in a step-by-step approach and establish this feasible and cost-effective strategy for schistosomiasis screening. The fact that these guidelines are based on studies in many countries means that they can be applied with some confidence in new places. Nevertheless, it was urged that further rigorous validation of the questionnaire technique should be carried out in some situations: (1) when the method was being used in a different endemic setting; (2) when the questionnaire had undergone significant changes; or (3) where strong arguments are needed to demonstrate to health authorities the attractiveness of this method in their own country (Chitsulo *et al.* 1995).

Although the guidelines were designed for direct application by the district health managers, the practical situation in Côte d'Ivoire showed that this alone was not sufficient for the technique to be applied directly on a wide-scale. The national schistosomiasis control manager was well aware of the questionnaire procedure, and wished its application on the national scale. However, it was considered by the national authorities that the guidelines were not "scientific" enough, and prior to widespread application of the questionnaire, a rigorous validation was requested. It was decided to carry this out in central Côte d'Ivoire. There was some evidence that this area is endemic for *S. haematobium*, but no systematic survey had yet been carried out (Doumenge *et al*. 1987). Furthermore, there was concern that *S. haematobium* prevalence among schoolchildren had risen to alarmingly high levels in villages located adjacent to Lake Kossou and Lake Taabo, two recently constructed man-made lakes (N'Goran *et al*. 1997). When the idea of the questionnaire was discussed with local

health and education authorities, they were impressed by the simplicity of the method. However, they also expressed considerable doubts as to whether this technique would provide accurate results in their own district.

The design of our study followed that of previous ones (Lengeler *et al*. 1991a, b, Red Urine Study Group 1995). After pre-testing the original version of the questionnaire in two villages, considerable changes were found to be necessary, as there were commonly perceived signs and symptoms typical for this epidemiological setting that were not included in the original questionnaire. Within 5 weeks, 92% of the schools returned completed questionnaires to the education secretary. The biomedical validation which was performed in a random sample of 60 schools, involved teacher's reagent stick testing and cross-checking of their results by our research team in a sub-sample of schools. In agreement with preceding studies, reagent sticks were a reliable means of assessing *S. haematobium* infections, and teachers' performance of the testing was competent. It is interesting to note that teachers were proud to receive a formal training during a one-day workshop on the use of reagent sticks. They gained a lot of satisfaction from collaborating actively in a health campaign in their school, and they were pleased that their assessment of microhaematuria was subsequently used for the basis of praziquantel treatment (N'Goran *et al*. 1998). This active participation of the teachers is a crucial point for the success of this method, and can contribute to the integration of schistosomiasis control measures into the routine primary health care system. It was also observed that teachers, and consequently also other members of the community, had become more aware about schistosomiasis in their village. Many teachers emphasised that they will integrate the experiences gained during the whole process into their curriculum and that they will designate a special lesson for dealing with schistosomiasis and means for control activities.

The results of this questionnaire validation were first discussed with the national schistosomiasis control coordinator, and then presented at a national conference assembling most regional health and education authorities of Côte d'Ivoire, in order to design an effective strategy to control schistosomiasis. After our thorough validation, there was now agreement about the usefulness of questionnaires for rapid screening of *S. haematobium*. It was suggested that questionnaires should subsequently by used as a first stage to map out the areas at highest risk of *S. haematobium*.

There was considerable discussion about how to extend the experiences gained with the questionnaire technique in one district of central Côte d'Ivoire to the national scale, for instance how all education officers could be reached most rapidly, and with the lowest possible cost. An innovative idea was developed and is currently being used in 5 out of 16 districts in Côte d'Ivoire. It relies on the active participation of University students and consists of six steps. (1) Students receive a formal training on the "indirect questionnaire approach". They are invited to study the WHO guidelines (Chitsulo *et al*. 1995). Then they learn how these guidelines were translated into the local situation in Côte d'Ivoire, on the basis of the published

results from the questionnaire survey and validation conducted in their country (N'Goran *et al*. 1998). (2) Students are equipped with an official letter signed by the national schistosomiasis control coordinator. They travel by public transport to the different regions to seek contact with the responsible health and education authorities. There, students present the idea of the questionnaire method and discuss the results obtained from central Côte d'Ivoire. Students ask for a copy of the school-list containing the names of all schools with the number of pupils enrolled in each of them. (3) Students return to the University and prepare questionnaires according to the list of schools. (4) Students travel back to the education secretary and deposit the questionnaires, which will subsequently be distributed through the existing channels. (5) Four to six weeks later, students again return to the education officer and collect the completed questionnaires that have been sent back to the education secretary. (6). Back at the University, students calculate the proportion of children with reported blood in urine and reported schistosomiasis and rank schools accordingly. So far, more than 1,300 primary schools have been enrolled in the first 5 districts in Côte d'Ivoire. The active participation of students should provide the basis for a rapid and inexpensive national ranking of the schools at highest risk of *S. haematobium* infection.

If it proves to be effective, this approach will be applied in the remaining 11 districts in Côte d'Ivoire. It experiences in Côte d'Ivoire is promising, this collaboration with university teaching departments could be extended to other African countries, and to other disciplines. For example, it could be integrated as a case study in courses in biology and/or medicine. There is also great potential to foster interdisciplinary research by integrating students from the mathematical department in such a case-study as well. These students would be responsible for data entry, data management and quality control. Finally, the geographical department could be associated, feeding the generated data of high risk communities into a geographical information system. Maps could be drawn, highlighting the high risk areas, so that treatment campaigns could be started in those communities.

11.3   The use and validation of questionnaires for *S. haematobium* in Nigeria

Linked to the on-going process of the questionnaire validation for larger-scale application in Côte d'Ivoire, there was a demand coming from Nigeria. The Ministry of Health in collaboration with the German Technical Co-operation were in the process of implementing a primary health care programme in Borgu Local Government Area (LGA), Niger State in north-western Nigeria. Records showed that *S. haematobium* was the predominant schistosome species in this area, and more widespread than *S. mansoni* (Cowper 1973, Istifanus *et al.* 1988, Awogun 1990). Most likely due to the construction of the Kainji dam reservoir in the eastern part of Borgu LGA, the prevalence of *S. haematobium* infection had risen and the disease was

perceived to be an important public health problem by many local communities. Schistosomiasis was given a high priority in the primary health care programme and the use of questionnaires was suggested as a first stage in a phased control programme. Consequently, our group was asked for support in validating the questionnaire technique in this epidemiological setting. Emphasis was on community diagnosis, but there was also interest in further investigating whether the technique could also provide reliable results for individual diagnosis. Results of the validation would allow a decision to be made in view of the widespread application afterwards.

The design of the study followed that of all previous ones, and the results confirmed that questionnaires are an accurate means for rapid identification of the communities at highest risk of *S. haematobium* in Nigeria (Mafe *et al*. 2000). There were two novel elements in this Nigerian study.

First, questionnaires were modified following a series of focus group discussions carried out with schoolchildren, teachers and health personnel. This was an effective approach and allowed commonly perceived signs and symptoms of *S. haematobium* to be identified. Focus group discussions had previously been used with success in Côte d'Ivoire to identify intestinal morbidity indicators to predict an infection with *S. mansoni* (Utzinger *et al.* 1998), and also amoebiasis infections (Utzinger *et al.* 1999).

Second, the design of the questionnaire followed an approach previously developed in Côte d'Ivoire (Utzinger *et al.* 2000), which allowed us to perform analysis at the community and also individual level. In principal, the easiest way to obtain children's individual responses is by using one questionnaire per child. However, when the number of children being interviewed is large, this becomes impractical and costly. The questionnaire studies performed so far interviewed between 2,918 and 19,362 children per setting (Lengeler *et al*. 1991a, b, Red Urine Study Group 1995, Booth *et al*. 1998, N'Goran *et al*. 1998, Utzinger *et al*. 2000). During one study carried out in Cameroon, a response-sheet for each child was used. It was found that this caused operational problems that largely outweighed the advantages of having the additional individual data, as there was a huge increase in the amount of paper used (more than 100 kg) and the cost of photocopies (Red Urine Study Group 1995). An alternative approach, reducing the costs of photocopies to a minimum was thus required. As the teachers had class lists with the names of their children in alphabetical order, we accompanied our questionnaire (1 page allowing for 50 children to be interviewed) with a blank class lists (consecutive numbers from 1-50). Teachers were invited to copy the children's names onto our blank list and then interview the children in the same order. This allowed individuals to be identified during data analysis.

Using a multivariate analysis and adjusting for potential confounding factors, such as sex, age and concurrent infection with other intestinal parasites, we calculated an odds ratio of 2.6 for the symptom "blood in urine" at the microhaematuria level of 1+. In other words, the risk that

a child who reports the presence of blood in urine is actually infected with *S. haematobium* is 2.6 times higher than that of a child who does not report this symptom. Although this correlation was significant, it is not so high that the symptom "blood in urine" could be recommended for individual diagnosis in this setting. For Tanzania, there is increasing evidence that reported blood in urine and/or reported schistosomiasis are useful indicators for an individual diagnosis of *S. haematobium* infections. In the Morogoro Rural District in south-central Tanzania, the association between the symptom "blood in urine" and an infection with *S. haematobium* resulted in an adjusted odds ratio of 7.7 (Booth *et al.* 1998). In two recent studies carried out in Mwanza District in the north-eastern part of Tanzania, it was found that reported blood in urine and reported schistosomiasis were good indicators for a self-diagnosis of infected individuals, especially those who had a heavy infection with more than 50 eggs/10 ml of urine (Ansell *et al.* 1997, Partnership for Child Development 1999).

It can be concluded that simple school questionnaires allow the rapid and inexpensive assessment of schools (communities) at highest risk of *S. haematobium* infections. There is increasing evidence that reported blood in urine is a useful sign for self-diagnosis. However, more research is needed to finally conclude whether this reported symptom could be used in school-based schistosomiasis control programmes.

11.4   The development and validation of a questionnaire technique for rapid screening of *S. mansoni*

There has been considerable discussion about possible ways of extending the questionnaire technique initially developed for urinary schistosomiasis to intestinal schistosomiasis due to *S. mansoni*. It is widely acknowledged that this is a complex issue, since clinical signs and symptoms indicating an infection with *S. mansoni* have generally shown only low sensitivity and specificity values. There is not one single sign or symptom that is uniquely associated with *S. mansoni*. This probably explains why the community perception of an *S. mansoni* infection is usually weaker than the perception of an *S. haematobium* infection. However, the benefits of having a rapid assessment procedure for *S. mansoni* would be considerable. Firstly, pathology caused by *S. mansoni* infections is generally more severe than that caused by *S. haematobium* infections. Secondly, there is accumulated evidence that *S. mansoni* is replacing *S. heamatobium* in many areas of sub-Saharan Africa and is therefore becoming more widespread (Hunter *et al.* 1993, Mott *et al.* 1995, Pervilhac *et al.* 1998).

Numerous epidemiological and hospital-based studies, carried out in African countries, have found a significant association between an *S. mansoni* infection and the presence of blood in stool and/or bloody diarrhoea at the individual level (Ongom & Bradley 1972, Cook *et al.* 1974, Arap Siongok *et al.* 1976, Hiatt 1976, Cline *et al.* 1977, Hiatt & Gebre-Medhin 1977, Sukwa *et al.* 1985, Proietti & Antunes 1989, Lima e Costa *et al.* 1991, Gryseels 1992, Rodrigues *et al.* 1995). These findings raised hope that asking children about the presence of blood in stool or the presence of bloody diarrhoea might provide a means for rapid screening.

Following this idea, three large-scale studies were carried out in the Democratic Republic of Congo (Red Urine Study Group 1995, Lengeler *et al.* 2000), Ethiopia (Hailu *et al.* 1995) and Tanzania (Booth *et al.* 1998). Questionnaires including questions about the symptoms "blood in stool" and "bloody diarrhoea" and the disease "schistosomiasis" were administered district-wide and the diagnostic performance of these questions was calculated. Although "blood in stool" and "schistosomiasis" were useful questions to identify schools that were at high risk of *S. mansoni* infection, the results were not conclusive enough to use as a basis for operational interventions.

In the framework of the ongoing process in Côte d'Ivoire of rigorous validation of the questionnaire technique for *S. haematobium*, we planned and carried out the development and validation of a similar questionnaire for rapid identification of *S. mansoni*. In close collaboration with the national schistosomiasis control programme, a series of studies were launched in western Côte d'Ivoire, an area highly endemic for *S. mansoni* (N'Goran *et al.* 1989). Our studies are probably the largest of their kind yet undertaken in Africa and the emphasis was on both individual and community diagnosis.

A first study was carried out to assess children's perception of intestinal schistosomiasis as a preliminary step to designing the questionnaire. This involved the active participation of 209 schoolchildren and 9 teachers from three primary schools. In a first step, schoolchildren were screened on four consecutive days to assess levels of *S. mansoni* infections. In a second step, heavily infected schoolchildren (> 400 *S. mansoni* eggs per gram of stool) were invited to participate in focus group discussions (FGDs). Two social scientists with a special background in medical anthropology conducted the FGDs following a pre-tested discussion line. FGDs proved to be an effective way to investigate the most commonly perceived indicators of intestinal morbidity due to *S. mansoni*. This method also allowed to probe for local terms in the local Yacouba and Dioula languages associated with *S. mansoni*. The symptoms "blood in stool" and "bloody diarrhoea" were frequently stated and the most common local terms for these two symptoms were "gnon" (Yacouba: "blood") and "tòtò" (Dioula: "bloody diarrhoea"). Children seemed to enjoy these FGDs. They laughed and were relaxed during the discussions, and expressed in a very open way what they experienced on a day-to-day basis in terms of intestinal complaints.

A comprehensive questionnaire was created including all these perceived morbidity indicators and teachers interviewed children individually. Comparison between the questionnaire responses and the levels of an *S. mansoni* infection revealed that the symptom "blood in stool" showed the best diagnostic performance to predict an infection. The local terms also showed a significant association with an *S. mansoni* infection; however teachers pointed out that these terms would be of little use in case of wide-scale application of the questionnaire, since other local languages are spoken in neighbouring villages.

This study revealed three additional important findings (Utzinger *et al.* 1998). First, there was a clear change in children's noticing of the symptom "blood in stool" at a cut-off level of 100 eggs per gram of stool. Interestingly, this is in full agreement with the cut-off proposed by WHO (1993), who classify infections below this cut-off as "light infections" and above as "moderate" to "heavy infections". Second, the usefulness of the symptom "blood in stool"

could be confirmed by comprehensive multivariate analysis which revealed that other concurrent intestinal parasite infections were not significantly associated with "blood in stool", therefore did not act as confounding factors. Third, children reported the symptom "blood in stool" significantly less often after praziquantel treatment.

Based on these positive findings a questionnaire was distributed and validation at the district level with emphasis both on individual and community diagnosis. For individual diagnosis, the study confirmed that the symptom "blood in stool" is significantly associated with an *S. mansoni* infection. However the adjusted odds ratio was only 1.6, which did not allow this symptom to be recommended for individual diagnosis. The diagnostic performance of the symptom "blood in stool" showed a low sensitivity (37%) and a moderate negative predictive value (51%). Comparison of these values with preceding studies revealed that our values are within the range of values estimated elsewhere (Table 11.1).

It has been suggested that low sensitivity of the symptom "blood in stool" could be partly explained by the confounding effect of concurrent intestinal parasites (Sukwa *et al.* 1985, 1986, Lima e Costa *et al.* 1991). This hypothesis could not be confirmed with our data from Côte d'Ivoire (Utzinger *et al.* 1998, 2000). Our findings are in agreement with recent data from Tanzania, where a substantial fraction of bloody stool episodes could be attributable to *S. mansoni* infections (Booth *et al.* 1998). This indicates that concurrent intestinal parasites are unlikely to affect the relationship between "blood in stool" and an infection with *S. mansoni*.

Table 11.1

Diagnostic performance of observed and/or reported blood in stool to detect an individual with an *S. mansoni* infection (PPV: positive predictive value, NPV: negative predictive value).

Country	Diagnostic performance (%)				Reference
	Sensitivity	Specificity	PPV	NPV	
Uganda	51.9	84.1	93.3	29.1	Ongom & Bradley (1972)
St. Lucia	40.0	56.5	82.1	15.9	Cook *et al.* (1974)
Kenya	13.0	90.4	88.5	15.4	Arap Siongok *et al.* (1976)
Ethiopia	11.0	96.1	88.9	27.7	Hiatt (1976)
Puerto Rico	12.8	96.0	76.0	52.4	Cline *et al.* (1977)
Ethiopia	11.7	93.8	93.3	12.4	Hiatt & Gebre-Medhin (1977)
Zambia	17.2	94.9	88.4	33.4	Sukwa *et al.* (1985)
Brazil	16.4	95.7	79.2	53.4	Proietti & Antunes (1989)
Brazil	12.7	97.5	77.8	61.4	Lima e Costa *et al.* (1991)
Brazil	18.6	87.3	60.0	51.3	Rodrigues *et al.* (1995)
Côte d'Ivoire	36.3	81.3	95.5	9.6	Utzinger *et al.* (1998)
Côte d'Ivoire	37.2	76.4	64.9	50.8	Utzinger *et al.* (2000)

When analysis was performed at the community (school) level, the prevalence of the two symptoms "blood in stool" and "bloody diarrhoea" correlated significantly with the infection prevalence of *S. mansoni* infection, which is in agreement with previous studies (Hailu *et al*. 1995, Red Urine Study Group 1995, Booth *et al*. 1998). Our study revealed low correlation coefficients and there was considerable variability in the data. It was interesting to note that these correlations could be improved if those schools with the highest sex ratios (predominance of boys) were removed from the analysis. This is an interesting finding for which we have no explanation at present, and it should be assessed in more detail in subsequent studies.

In conclusion, our questionnaire showed only a moderate diagnostic performance. Therefore, this questionnaire, relying on the results of perceived symptoms alone, is insufficient to identify individuals and/or communities at highest risk of *S. mansoni* infection, and could not be recommended for large-scale application in Côte d'Ivoire.

It was argued that a combination of perceived symptoms and other risk factors could increase the diagnostic performance of questionnaires. Therefore, a third study assessed whether the diagnostic performance of our questionnaire could be improved by asking children also about water contact patterns for occupational and/or recreational reasons. The study revealed that water contact patterns were better predictors than perceived symptoms to identify an infection with *S. mansoni*. Three general water contact patterns showed a significant association with an increasing level of *S. mansoni* infections: (1) crossing rivers, (2) swimming/bathing and (3) fishing with nets. Further analysis using a multivariate approach showed that more specific questions, asking also about the locations where these activities were performed, increased the adjusted odds ratios considerably. One river could be identified as the most likely source where *S. mansoni* transmission is occurring. Although this finding is of relevance for the population studied, it is not possible to generalise this result for other settings.

Our findings that particular water contact patterns are good predictors for an *S. mansoni* infection are in good agreement with previous studies conducted in Kenya (Kloos *et al*. 1997), Nigeria (Useh & Ejezie 1999) and also in Brazil (Lima e Costa *et al*. 1987, 1991, Barreto 1991, Firmo *et al*. 1996). Another interesting study conducted in Tanzania revealed that five particular water habitat features (type of water body, water velocity pattern, type of bottom of habitat, pattern of desiccation, presence of floating vegetation) were strong predictors for a transmission site of *S. mansoni*. Most interestingly, children were able to recognize these habitat features and could therefore correctly identify a probable transmission site (Odermatt 1994). It has been shown that such knowledge can later be used to tailor effective health education materials that are well adapted to local conditions and might help to modify children's behaviour by encouraging them to avoid potentially dangerous transmission sites (Useh & Ejezie 1999).

However, although recalled water contact patterns were better predictors than questions about perceived symptoms, the diagnostic performance was still only moderate. For the time being, questionnaires cannot be recommended for rapid screening to identify individuals or communities at highest risk of infections with *S. mansoni*.

11.5 Prophylactic effect of oral artemether against *S. mansoni*

The identification of individuals and/or communities at high risk of schistosome-related morbidity is a first step in the management and implementation of cost-effective schistosomiasis control programmes. Since there is no vaccine available at present (Bergquist 1998, Capron 1998, Gryseels 2000), the next step is treatment of infected individuals with an effective drug. It has been found that successful morbidity control requires an effective initial treatment, as well as the prevention of re-infection. This calls for long-term commitment to control measures, and in case of re-infection, requires repeated community-based treatment campaigns (Gryseels 1989). It has been shown that repeated treatment is a feasible strategy, and effectively reduces the prevalence and intensity of infection over time (Gryseels *et al*. 1991, Engels *et al*. 1993, Boisier *et al*. 1998, Pervilhac *et al*. 1998). Using ultrasound, it has also been demonstrated in children that after treatment, most morbidity due to schistosomiasis is reversible. Studies carried out in Tanzania and Ghana revealed that nearly all bladder and urinary tract pathology resolved after praziquantel treatment of children infected with *S. haematobium* (Hatz *et al*. 1990, 1998, Wagatsuma *et al*. 1999). In a study conducted in Madagascar, there was improvement of liver pathology and prevention of the development of schistosomal hepatic fibrosis in *S. mansoni* infected children after praziquantel treatment. The required frequency of re-treatment depends on the epidemiological setting. Two recent studies carried out in *S. haematobium* endemic areas revealed a considerable amount of urinary tract pathology. Following a cohort of children after praziquantel treatment over 18 to 24 months showed that in these two settings a treatment every two years would be sufficient to control morbidity (Hatz *et al*. 1998, Wagatsuma *et al*. 1999).

Currently, the drug of choice for chemotherapy is praziquantel, which is effective against all schistosome species (WHO 1993). Recently, there has been considerable concern that tolerance and/or resistance to praziquantel might exist or is being developed (Cioli 1998). Three independent observations form the basis for suspicion of praziquantel tolerance/resistance. Firstly, in a community recently exposed to a very intense focus of *S. mansoni* in northern Senegal, the recommended standard treatment with 40 mg/kg praziquantel showed unexpected low cure rates of only 18-36% (Gryseels *et al*. 1994, Stelma *et al*. 1995). Increasing the dose to 60 mg/kg failed to show a significant improvement (Guissé *et al*. 1997). Interestingly, treatment with 20 mg/kg oxamniquine, an alternative drug, gave a

significantly higher cure rate of 79% (Stelma *et al.* 1997). Secondly, a large-scale intervention was carried out in Egypt, with almost 2,000 subjects treated with 40 mg/kg praziquantel. Six to eight weeks later, patients were re-examined and those with a positive result received 60 mg/kg praziquantel. The remaining positive subjects received again 60 mg/kg praziquantel. After this third dose, there were still 46 patients who excreted eggs. When schistosome isolates of these subjects were compared with those of patients successfully treated in a laboratory test with praziquantel, significantly higher ED_{50} values were observed (Ismail *et al.* 1996, Bennett *et al.* 1997). Thirdly, the possibility of selecting schistosomes largely insensitive to praziquantel after the administration of several subcurative doses given to a laboratory strain of *S. mansoni* could be demonstrated (Fallon & Doenhoff, 1994). Interestingly, these experimental results could be confirmed with one isolate of *S. mansoni* obtained from snails in the Senegalese focus, who showed a significantly lower susceptibility to praziquantel, when compared with other laboratory isolates obtained from elsewhere (Fallon *et al.* 1995).

It is, however, important to note that the low cure rates with praziquantel found in northern Senegal might also be explained differently. The extremely high infection intensity, the maturation of prepatent *S. mansoni* infections and probably also immunological factors might be alternative explanations to praziquantel tolerance or resistance. However, these observations call for a careful monitoring of the effectiveness of praziquantel in the field and further laboratory experiments (Cioli 1998, Kusel & Hagan 1999).

At present, there are two alternative antischistosomal drugs. Metrifonate which is effective against *S. haematobium*, and oxamniquine which is effective against *S. mansoni* (WHO 1993). However, it has been observed that these two drugs have become difficult to procure in many African countries. The importance of actively pursuing research and development of novel antischistosomal drugs cannot be overemphasised (Cioli 1998).

Artemether, a semisynthetic derivative of the naturally occurring sesquinterpene lactone found in a traditional Chinese herbal remedy, *Artemisia annua* (L.), is another drug that has been shown to have antischistosomal properties (Le *et al.* 1982) It is already known to be safe for use in humans. In the first laboratory experiments, mice infected with adult *S. japonicum* received oral artemether over a 1- to 4-day course with a total dose of 400 to 800 mg/kg, and high worm reduction rates between 55% and 80% were observed (Le *et al.* 1982). In the same work it was already noted that 7-day-old parasites were especially susceptible to artemether, but not 14- or 21-day old parasites. In subsequent studies, it was confirmed that immature worms were most susceptible to artemether. In a series of laboratory experiments with *S. japonicum*-infected rabbits, the highest worm reduction rates were observed in 5- to 14-day-old parasites, whereas significantly lower worm reduction rates were observed in both younger and older worms (Table 11.2; Xiao *et al.* 1995). These laboratory studies led to the conclusion that artemether is most active against the juvenile stages of *S. japonicum* and that it is most effective when given between days 7 and 14 after an infection with *S. japonicum*.

Subsequently, field trials were launched with oral artemether given at repeated doses with intervals of two weeks. So far, artemether was used in 7 randomized clinical trials conducted in China with more than 4,500 humans exposed to *S. japonicum*. Results revealed firm evidence that artemether shows a significant effect on *S. japonicum* infections. Repeated oral artemether at a dose of 6 mg/kg for a total of 2-10 doses, covering half or the entire transmission period, was well tolerated and reduced the incidence by 60-100% (Xiao *et al*. 2000a). Such a use of artemether was defined as chemoprophylaxis. Since artemether kills immature worms, it prevents the development of the mature egg-laying female worms which cause damage to the human host as a result of egg secretion.

Based on the prophylactic effect that artemether showed against *S. japonicum*, it was hypothesized that it might have a similar effect against *S. mansoni*. In a series of laboratory experiments with *S. mansoni*-infected mice, artemether was given orally at different intervals after infection. The highest worm reduction rates were observed when the drug was given 14-21 days after infection (83-98%). When artemether was administered later, 28 or 42 days after infection, it showed significantly lower worm reduction rates of 63% and less than 50%, respectively (Table 11.2; Xiao & Catto 1989). In another series of experiments, mice and hamsters were infected with *S. mansoni* and treated with artemether at day 45 after infection. The observed worm reduction rates were low: 23-51% in mice, and 30-39% in hamsters. Therefore, these results confirmed that adult *S. mansoni* worms are less susceptible to artemether than immature worms (Araujo *et al*. 1991). Recently, another series of laboratory experiments were carried out with *S. mansoni*-infected mice. The highest worm reduction rates were again observed in 7- to 21-day-old worms (Table 11.2; Xiao *et al*. 2000b).

Since laboratory experiments had clearly demonstrated the prophylactic effect of artemether against morbidity due to *S. mansoni* infection, oral artemether was evaluated in a randomized clinical trial. The study carried out in an *S. mansoni* endemic area in Côte d'Ivoire confirmed that oral artemether is safe and has a prophylactic effect. An incidence that was 50% lower (95% CI: 35-71%) was calculated for those children who received artemether. There was also a significant reduction in the intensity of *S. mansoni* infection among positive children who had received artemether. The reduction in incidence of infection in our study was lower than in the field trials with *S. japonicum* in China, but trials with different parasites and in different endemic settings cannot be directly compared.

Table 11.2

Effect of oral artemether on different developmental stages of *S. japonicum* (a) or *S. mansoni* (b and c). NA=not assessed.

Age of worm (days)	*S. japonicum*-infected rabbits (a)		*S. mansoni*-infected mice (b)		*S. mansoni*-infected mice (c)	
	Total worms	WRR	Total worms	WRR	Total worms	WRR
Control	128 ± 11	–	41.7 ± 11.3	–	17.8 ± 9.4	–
3	109 ± 18	14.3	37.2± 8.3	10.8	NA	NA
5	13 ± 13	90.0	NA	NA	11.9 ± 4.5	23.2
7	9 ± 7	93.0	12.5 ± 7.3	70.0	7.8 ± 2.9	56.2
9	13 ± 13	90.0	NA	NA	NA	NA
11	8 ± 4	94.0	NA	NA	NA	NA
14	13 ± 13	90.0	7.2 ± 4.5	82.7	4.4 ± 4.2	75.3
17	31 ± 8	75.8	NA	NA	NA	NA
21	40 ± 6	68.7	4.2 ± 2.9	89.9	3.2± 3.5	82.0
28	89 ± 8	30.8	15.4 ± 10.3	63.1	6.2± 3.3	65.2
35	95 ± 8	25.8	20.5 ± 7.7	50.8	9.1± 6.2	48.9
42	NA	NA	29.3 ± 5.4	29.8	NA	NA

a) Rabbits infected with 198-202 *S. japonicum* cercariae. Artemether given intra-gastrically, single dose of 15 mg/kg (Xiao *et al*. 1995)

b) Mice infected with 100-150 *S. mansoni* cercariae by subcutaneous injection. Artemether given orally at 300 mg/kg (Xiao & Catto 1989)

c) Mice infected with 60 *S. mansoni* cercariae by subcutaneous injection. Artemether given orally at 400 mg/kg (Xiao *et al*. 2000b)

In view of preceding laboratory studies with animals experimentally infected with *S. japonicum* or *S. mansoni* it was clearly shown that artemether is most potent in killing immature worms. This is in contrast to praziquantel and other alternative antischistosomal drugs that are most active against adult worms (Sabah *et al*. 1986). This observation might be of considerable importance for schistosomiasis control measures, since a combination therapy with praziquantel and artemether may result in higher cure rates. Recent preliminary laboratory studies with mice infected with *S. mansoni* at different developmental stages (immature and adult worms) and treated with both drugs showed very high worm reduction rates (Xiao Shuhua & Jacques Chollet, personal communication). This finding is promising, however more research is requested to evaluate whether such a combination therapy is safe. A combined treatment might also reduce the risk of developing drug resistance, a strategy already widely used for other infectious agents.

Since artemether has been shown to be active against *S. japonicum* and *S. mansoni* it was considered worthwhile to test its prophylactic effect against *S. haematobium* infection. The first preliminary results of a series of laboratory experiments confirm the prophylactic effect of artemether against *S. haematobium* infection (Xiao Shuhua & Jacques Chollet, personal communication). We have therefore planned a field trial to assess its efficacy in controlling infection with *S. haematobium* in humans.

While our field trial showed a prophylactic effect of artemether against *S. mansoni* infection in humans, there are several important questions to be addressed and discussed before there is any wider application. The most important concern is the risk of developing artemether resistance in *Plasmodium falciparum*. When we conducted our field trial and gave six doses of oral artemether (6 mg/kg) at intervals of 3 weeks, some effect was to be expected against malaria parasites. In fact, a significant reduction in the prevalence of *P. falciparum* and a significant increase in the packed cell volume was observed in artemether recipients. Artemether is very effective against severe malaria and multi-drug-resistant falciparum malaria (Klayman 1985, Hien & White 1993, White 1994, White *et al*. 1999). Therefore it is of pivotal importance that it should remain effective, and should not be used in any way that might lead to resistance developing in the malaria parasite.

At present, in areas where *S. mansoni* is co-endemic with malaria, artemether should not be recommended for large-scale prophylactic use against *S. mansoni*. However, in areas where malaria is absent, such as large parts of Egypt and Brazil, the use of artemether could be recommended as an additional tool in the control of schistosomiasis. Another potential application of artemether could be envisaged for a short and limited time period, in remaining *S. mansoni* foci where transmission is low and the disease is close to eradication. Finally, artemether could be used for prophylaxis in particular circumstances: (1) Workers who cannot avoid exposure to highly *S. mansoni* infested water sources (e.g. canal cleaners in irrigation systems in the Sudan). (2) Previously-unexposed people who may come into contact with infected water, such as flood-relief workers or travellers.

Our findings will therefore stimulate the discussion on the use of artemether in schistosomiasis control activities and we believe that artemether (and hopefully also novel drugs yet to be discovered) may help to tailor more effective measures for schistosomiasis control, adapted to specific epidemiological settings.

11.6 Conclusion

Novel approaches in the control of schistosomiasis were investigated mainly in areas endemic for *S. haematobium* and *S. mansoni* in Côte d'Ivoire. Larger scale application of a questionnaire procedure for rapid identification of *S. haematobium* was the starting point of the work. Linked to this process, possible ways of extending this approach to *S. mansoni* were assessed by development and validation of a questionnaire for rapid screening of individual and/or communities at highest risk of infection. Finally, in an area highly endemic for *S. mansoni*, the prophylactic effect of oral artemether against *S. mansoni* infections was assessed. Based on a series of eight studies, the following main conclusions could be drawn.

1. Côte d'Ivoire is the first country that has taken advantage of the WHO guidelines for rapid identification of high risk communities of *S. haematobium* in a national programme. After successful validation of the questionnaire technique in one district, the results were widely discussed and presented to district authorities of the health and education sectors. The method is now being extended and applied on a large scale, covering 5 out of 16 districts in Côte d'Ivoire. The results of this exercise will be of great importance in elaborating final recommendations for a national schistosomiasis control strategy, which may also be of use in other African countries.

2. A demand-driven request from Nigeria was addressed to us during on-going work in Côte d'Ivoire. The excellent performance of the "indirect questionnaire approach" for rapid screening of *S. haematobium* could be confirmed in this epidemiological setting and the method is being recommended for application as a first step in the state-level schistosomiasis control programme.

3. Schoolchildren living in an *S. mansoni* endemic area have a clear perception of intestinal morbidity caused by this disease and the two symptoms "blood in stool" and "bloody diarrhoea" were both found to be associated with an infection.

4. The largest study yet undertaken in Africa designed and evaluated a questionnaire for rapid screening of high risk individuals and/or communities of *S. mansoni*. Although the symptoms "blood in stool" and "bloody diarrhoea" correlated with an *S. mansoni* infection, both at the individual and at the community level, the diagnostic performance of the questionnaire was only moderate. Further development is needed before this technique can be recommended for large-scale application.

5. Oral artemether is safe and its prophylactic effect against *S. japonicum*, already documented in field trials in China, could also be confirmed against *S. mansoni* in the first randomized double-blind placebo-controlled trial. The use of artemether as an additional tool for a more comprehensive strategy of schistosomiasis control should be considered for particular epidemiological settings.

11.7   References

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Curriculum Vitae

I was born on 20August 1968 in Zurich, Switzerland, as son of Hansueli Utzinger and Silvia Utzinger-Häfeli. Between 1975 and 1981, I attended primary school in Erlenbach (ZH). After two years of secondary school also in Erlenbach, I attended high school in Zurich, where I completed in September 1987 with a degree in natural science.

In 1988, I absolved my required military training and in the same year, I entered the Swiss Federal Institute of Technology in Zurich (ETHZ), to study Environmental Science with special emphasis on Aquatic Biology. In October 1993, I obtained my Masters of Science degree from the ETHZ in Environmental Science. During my diploma work, I assessed the effects of environmental parameters on the distribution of a small benthic fish species, which had been carried out at the Limnological Research Centre of the Swiss Federal Institute for Environmental Science and Technology, under the supervision of Dr. Armin Peter.

Between 1993 and 1995, I attended the Postgraduate Course on Developing Countries (NADEL) offered by the ETHZ. The practical field assignment to complete the NADEL course was conducted at the Ifakara Health and Development Centre in Tanzania, where I worked for one year. I contributed to the evaluation of a multisectorial and integrated communicable disease control programme, with special emphasis on schistosomiasis control. I also had a chance to study the ecology of *Biomphalaria pfeifferi*, the intermediate snail host of intestinal schistosomiasis.

Between 1995 and 1996, I attended courses on Didactics and Pedagogy at the ETHZ and subsequently obtained a Teaching Degree in both environmental science and biology.

It was in mid 1996, when I joined the Swiss Tropical Institute in Basel as a research assistant, and developed the proposal for the present PhD thesis under the supervision of Prof. Dr. Marcel Tanner and PD Dr. Christian Lengeler.

During my studies I attended courses given by the following lecturers:

H. Ambühl, D. Ammann, N. Amrhein, W. Angst, P. Baccini, M. Baltisberger, K. Bättig, R. Baumgartner, H. Belevi, G. Benz, H. Brunner, E. Buff-Keller, H.P. Bürgi, R. Camenzind, K.H. Delhees, A. Einsele, A. Fischlin, H. Flühler, K. Frey, P.M. Frischknecht, A. Frutiger, R.K. Furrer, R. Gächter, C. Gessler, O. Ghisalba, W. Giger, A. Gigon, M. Glinz, D. Groh, K. Grossenbacher, R. Häsler, H.K. Hegetschweiler, G. Hirsch, R. Högger, W. Huber, D. Imboden, S. Ingrisch, R. Jagmetti, R. Kappel, J. Koella, F. Klötzli, T. Koller, B. Krüsi, H.R. Künsch, R. Kyburz-Graber, E. Landolt, T. Leisinger, C. Lengeler, F. Leutert, J. Marti, K. Meier, R. Müller, U. Müller-Herold, A. Peter, P. Schmid-Hempel, W. Schneider, R. Schwarzenbach, R. Senti, H.C. Siegmann, L. Sigg, V. Singeisen-Schneider, T.A. Smith, H. Sticher, F. Stolz, P. Suter, M. Tanner, H.R. Thierstein, K. Urbanska, A. Waldvogel, B. Wechsler, N.A. Weiss, H. Weiss, F. Widmer, O. Wildi, R. Zingg

List of publications

1. Utzinger J, Mayombana C, Mez K & Tanner M (1997). Evaluation of chemical and physical-morphological factors as potential determinants of *Biomphalaria pfeifferi* (Krauss, 1848) distribution. *Memorias do Instituto Oswaldo Cruz*, **92**: 323-328.

2. Utzinger J, Mayombana C, Smith T & Tanner M (1997). Spatial microhabitat selection by *Biomphalaria pfeifferi* in a small perennial river in Tanzania. *Hydrobiologia*, **356**: 53-60.

3. N'Goran EK, Diabate S, Utzinger J & Sellin B (1997). Changes in human schistosomiasis levels after the construction of two large hydroelectric dams in central Côte d'Ivoire. *Bulletin of the World Health Organization*, **75**: 541-545.

4. Utzinger J, Roth C & Peter A (1998). Effects of environmental parameters on the distribution of bullhead *Cottus gobio* with particular consideration of the effects of obstructions. *Journal of Applied Ecology*, **35**: 882-892.

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6. N'Goran EK, Utzinger J, Traoré M, Lengeler C & Tanner M (1998). Identification rapide par questionnaire des principaux foyers de bilharziose urinaire au centre de la Côte d'Ivoire. *Médecine Tropicale*, **58**: 253-260.

7. Pervilhac C, Mshinda H, Utzinger J, Booth M, Tanner M (1998). Experiences with a multi-sectorial operation research programme for control of schistosomiasis in a Tanzanian district. *African Journal of Health Sciences*, **5**: 153-160.

8. Booth M, Mayombana C, Machibya H, Masanja H, Odermatt P, Utzinger J & Kilima P (1998). The use of morbidity questionnaires to identify communities with high prevalences of schistosome or geohelminth infections in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **92**: 484-490.

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10. Utzinger J, N'Goran EK, N'Dri A, Lengeler C, Xiao SH & Tanner M (2000). Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. *Lancet*, **355**: 1320-1325.

11. Utzinger J, N'Goran EK, Ossey YA, Booth M, Traoré M, Lohourignon KL, Allangba A, Ahiba LA, Tanner M & Lengeler C (2000). Rapid screening for *Schistosoma mansoni* in western Côte d'Ivoire using a simple school questionnaire. *Bulletin of the World Health Organization*, **78**: 389-398.

12.   Utzinger J, N'Goran EK, Tanner M & Lengeler C (2000). Simple anamnestic questions and recalled water contact patterns for self-diagnososis of *Schistosoma mansoni* among schoolchildren in western Côte d'Ivoire. *American Journal of Tropical Medicine and Hygiene* (in press).

13.   Utzinger J & Tanner M (2000). Microhabitat preferences of *Biomphalaria pfeifferi* and *Lymnaea natalensis* in a natural and a man-made habitat in south-eastern Tanzania. *Memórias do Instituto Oswaldo Cruz* (in press).

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