

**Systems epidemiology of snail-borne diseases:
from methodological to social-ecological considerations in
the fight towards elimination**

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Für Dich!

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“Independence’ is a magic word, because nowhere in the Cosmos does it actually exist.” — Gabriel Brunsdon

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1. Summary

Background: Snail-borne trematode infections, including schistosomiasis and fascioliasis, affect an estimated 250 million and 2.4 million people worldwide, respectively. Health implications range from asymptomatic infections to severe morbidity, developmental and cognitive impairment, thus affecting the current and later life of infected individuals. Nonetheless, snail-borne trematodiasis in general, and fascioliasis in particular, remain among the most neglected of the neglected tropical diseases. The occurrence of these parasitic liver- and blood-fluke infections depend on a myriad of interrelating factors comprising a complex system of disease and health. A key feature pertains to the availability of suitable aquatic snail intermediate hosts from the family of the *Lymnaeidae* (for schistosomiasis) and *Planorbidae* (for fascioliasis). The distribution of these intermediate host snails, in turn, depends on ecological and environmental factors of their habitats, whereas these habitats are shaped by humans. The construction of dams, for example, extends the suitable habitats for intermediate host snail species and has been implicated with the spread and intensification of schistosomiasis. Furthermore, socio-economic and cultural factors as well as behaviour largely determine the extent of risky water contact including direct and indirect consumption and thus govern the risk of becoming infected with *Schistosoma* and *Fasciola*. Prevailing habits and social beliefs as well as knowledge and education likewise influence water contact patterns and health seeking behaviour. Individual immunology plays a role in acquiring infections and subsequent development of the disease for individuals exposed to these fluke infections. The nature of the interrelations in snail-borne trematode infections are complex and widespread. In order to eliminate snail-borne trematodiasis, especially schistosomiasis, efforts in the domains from innovation to application need to be increased covering all aspects of the whole system.

Goal and specific objectives: The overarching goal of this PhD thesis was to obtain a systems overview of schistosomiasis and – to some extent – fascioliasis in

the northern area of Côte d'Ivoire, placing particular emphasis of disease prevalence, social-ecological systems and methodological considerations. Specific objectives include: (i) to evaluate and improve currently existing tools for the assessment of infection within the communities ranging from household sampling to the validation of two rapid-diagnostic test within the setting; (ii) to elucidate prevailing water contact pattern and underlying reasons thereof alongside other factors leading to an increased risk of acquiring snail-borne trematodiasis for the local communities in northern Côte d'Ivoire; and (iii) to assess the distribution and ecological determinants of aquatic snail species serving as intermediate hosts for schistosomiasis and fascioliasis and relating it to the prevalence of infections within the human communities using these water sources.

Methods: A literature review was performed to identify suitable household sampling methods for situations where sampling frames are not available. Identified and newly proposed sampling methods were simulated over 250 iterations to identify features or the resulting samplings and assessing the amount of oversampling, systematic household exclusion as well as clustering.

For the studies involving fieldwork, a total of forty villages were randomly selected for participation. The study protocols received clearance from the ethics committees of Basel (EKBB, reference no. 64/13) and the national ethics committee in Côte d'Ivoire (reference no. 32-MSLS/CNERdkn). In Chad, research authorization including ethical approval was granted by the

District, regional and local authorities, village chiefs, study participants and parents/guardians of individuals aged below 18 years were informed about the purpose, procedures and potential risks and benefits of the study. Written informed consent was obtained from all participants and the parents/guardians of minors. Parasitological examinations as well as questionnaire surveys, focus group discussions and direct observations were performed within the villages, nearby Peulh settlements and surrounding water bodies. Parasitological examinations included reagent strip testing with Hemastix®, (Bayer Diagnostics; Basingstoke, United Kingdom), urine filtration of 10 ml of urine, double Kato-Katz of a single stool sample, Baerman filtration and the point-of-care circulating cathodic antigen test.

Snails and water parameters were collected from water sites indicated by the communities as the ones most frequently accessed by the population.

Results: Our literature review revealed 21 methods for household sampling and/or the creation or update of sampling frames. Some methods describe variations of cluster sampling, some aiming at the creation/obtaining or improving of existing sampling frames and some pertaining to achieve sampling in the absence of a sampling frame. Three methods pertained to sampling with rather strict requirements in surveys. A preliminary computer simulation of several existing and newly proposed spatial methods for household sampling revealed that all sampling methods based on a spatial approach oversampled houses around the starting point. Additionally many also systematically excluded certain households. One newly proposed method which employs the simple to implement use of a pouch of numbered paper lots is an adaption of the method from the extended programme of immunization (EPI). Equally sized and shaped paper lots containing numbers ranging from 1 to 20 are put into the pouch. An additional 21st lot is included, indicating that a new walking direction will have to be chosen randomly by spinning a bottle. This method delivered the best sample in the simulations, whereas several methods developed to improve the original EPI methods actually had worse outcomes compared to the original EPI method. A decision frame for choosing an adequate household sampling method for researchers and other individuals conducting surveys is proposed in the respective chapter.

The prevalence of schistosomiasis in the Tchologo region of northern Côte d'Ivoire was very low; Infections with *S. haematobium* and *S. mansoni* infections were found in 2.2% and 1.0%, respectively. No human *Fasciola* infection was found. With a prevalence of 13%, microhaematuria, as assessed with reagent strips, far surpassed the prevalence of *S. haematobium* determined with urine filtration in the study region. Our literature review revealed that in many published surveys, microhaematuria-positive test results that were not linked to positive urine filtration results occurred irrespective of the underlying *S. haematobium* prevalence assessed by urine filtration. These findings indicate either the occurrence of alternative causes

for blood in urine in endemic settings or the gross underestimation of the true prevalence of *S. haematobium* in various settings.

All individuals in our study villages had access to, and were using, safe water sources. Nevertheless, accessing and consuming unsafe water was very common and occurred in most instances during work on the fields or at the side of the road where it was unfeasible to transport needed quantities of drinking water and/or where water from the dams, rivers and small water collections was needed for the work. Additionally we could show that 38% of direct physical contact with unsafe water resulted from the fact that people who otherwise reported to only use safe water sources had to cross open water and thus increase the risk of acquiring schistosomiasis, albeit adequate water supply and sanitation facilities.

Intermediate host snail species were present in the study area, with fascioliasis intermediate host snails from the family of the *Lymnaeidae* occurring mostly in the northern part of the region, whereas *Schistosoma mansoni* transmitting *Biomphalaria* snails occurred mostly in the southern region, while *Bulinus* (intermediate host of *S. haematobium*) were ubiquitous. Human and animal presence at the water sites strongly correlated with snail occurrence.

Conclusions: The adoption of a systemic approach for the control and elimination of snail-borne trematodiasis can be very helpful, as it allows inclusion and consideration of a myriad of factors, ranging from methodological to social-ecological issues. Furthermore, researchers and intervention programmes could benefit from an even greater collaboration between different scientific fields, including but not limited to epidemiology, parasitology, sociology, anthropology and social psychology. Indeed, understanding the factors which make humans act in a certain desired or undesired way can play a major role in the success of control or elimination efforts. Most notably, the largest potential benefit could arise from working together with social marketers and drawing upon their years of experience in adequately identifying and analysing target populations and designing ways to tailor implement and communicate public health programmes/messages in a way that maximises community interest and incentives to adopt and sustain the programmes.

2. Introduction

2.1 Distribution and disease burden of the snail-borne trematodes schistosomiasis and fascioliasis

Snail-borne trematode infections including schistosomiasis, fascioliasis fasciolopsiasis, paragonimiasis, opisthorchiasis and angiostrongyliasis are estimated to affect 300 Million people worldwide (Adema et al., 2012). The two most important of these diseases, and the focus of this PhD thesis, are schistosomiasis which alone accounts for 240 Million infections, and fascioliasis which has the widest known longitudinal, latitudinal and altitudinal distribution of any vector-borne disease (Mas-Coma, 2004; WHO, 2008).

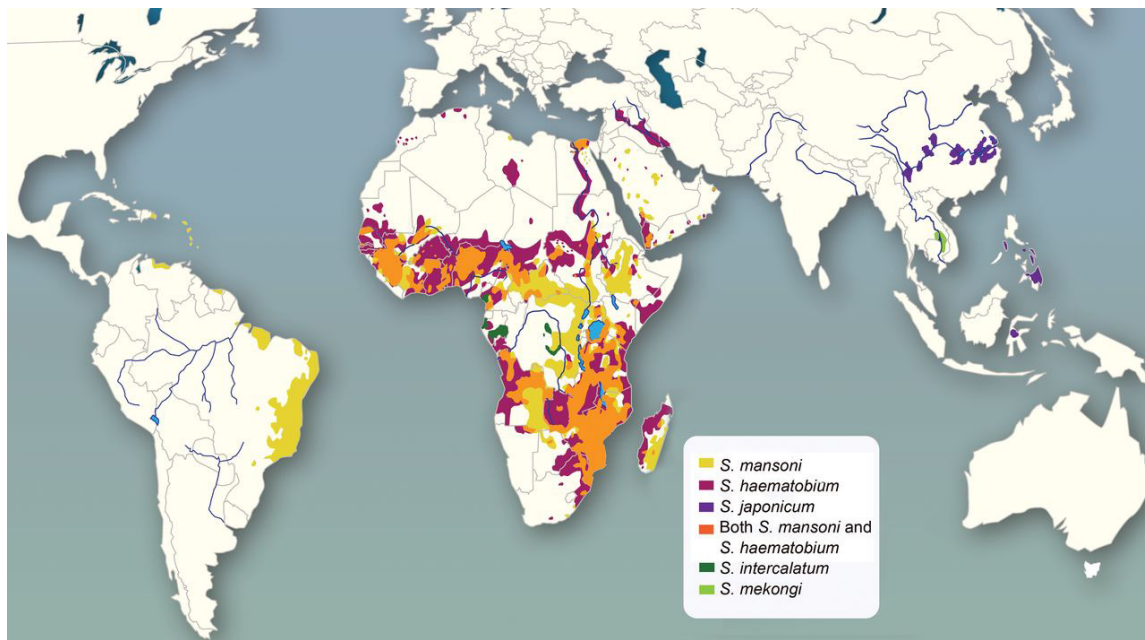
Schistosomiasis is endemic in 78 countries mostly in tropical and sub-tropical climates of sub-Saharan Africa, South America and Southeast Asia. While *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma intercalatum* are found mainly in sub-Saharan Africa, the middle east and some islands in the Indian ocean, as well as in south America and the Caribbean, *Schistosoma japonicum*, *Schistosoma guineensis*, *Schistosoma malayensis* and *Schistosoma mekongi* are predominantly found in south east Asian countries (Ross et al., 2002; Utzinger and Keiser, 2004b). More than half of all endemic countries are located in Africa (Bruun and Aagaard-Hansen, 2008). Figure 1.1 shows a map with the global distribution of human schistosomiasis.

Côte d'Ivoire, the study site of this PhD thesis, is endemic for both intestinal and urogenital schistosomiasis with local prevalence rates between <5% in the north, and 25-50% in the south and central part of the country (Utzinger et al., 2011; Scholte et al., 2014). An estimated 3.7 million Ivoirians are infected with schistosomiasis (WHO, 2010, 2013b).

In most high-income countries, schistosomiasis used to be limited to returning travellers and immigrants from endemic countries (Whitty et al., 2000; Grobusch et al., 2003). However, recent reports have shown that *S. haematobium* has been successfully introduced and has established itself in Corsica, France where several

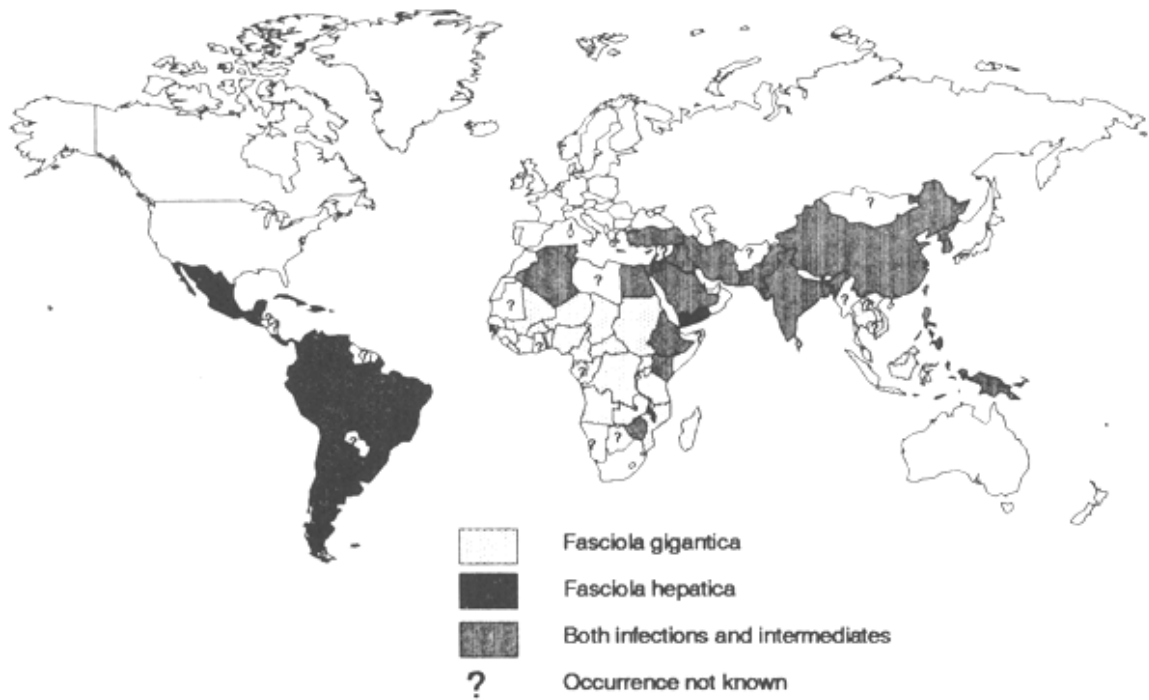
individuals acquired the disease from swimming in a local water body (de Laval et al., 2014; Boissier et al., 2015).

Fascioliasis is predominantly a zoonotic disease mainly affecting domestic ruminants but also pigs, rodents and other reservoir hosts (Mas-Coma et al., 1988). Human fascioliasis is an emerging health concern with raising numbers of infection and human infections have been diagnosed on all continents (Esteban et al., 1998; Mas-Coma, 2004). A map depicting human *Fasciola* infections can be seen in figure 1.2. Almost half of the reported infection with human fascioliasis occurs in African countries (Fürst et al., 2012). Within the African continent, *F. hepatica* and *F. gigantica* show different distributions with *F. gigantica* being more prevalent in the tropical regions whereas *F. hepatica* is more prevalent in the northern, Mediterranean and the southern African temperate regions as well as in high altitudes of Kenya and Ethiopia (Dorny et al., 2009). There is no data on the distribution of human or animal fascioliasis in Côte d'Ivoire. Animal surveys have been performed in the north where livestock production is common (Achi et al., 2003a; Achi et al., 2003c).



Weerakoon et al. 2015 Clin. Microbiol. Rev. 28:939-967

Figure 2.1 Global distribution of human schistosomiasis



<http://www.fao.org/docrep/004/t0584e/t0584e03.htm>

Figure 2.2 Global distribution of human fascioliasis

2.2 Burden of disease through schistosomiasis and fascioliasis

2.2.1 Schistosomiasis

It is estimated that 240 million people from at least 76 countries are worldwide infected with schistosomiasis of which 120 million suffer from related symptoms and 20 million from severe morbidity caused by the parasite. In total, 500 million are considered to be at risk for schistosomiasis infection (Ross et al., 2002; van der Werf et al., 2003; Grimes et al., 2015). Approximately 3.3 million disability adjusted life years (DALYs) are attributed to infections with *Schistosoma* spp. (Murray et al., 2012). In sub-Saharan Africa alone, the number of infected individuals amount to 163 million (Lai et al., 2015). Deaths related to schistosomiasis in sub-Saharan Africa amount to 280'000 per year (van der Werf et al., 2003; WHO, 2013b).

At least 261 million people required preventive treatment for schistosomiasis in 2013 (WHO, 2015).

2.2.2 Fascioliasis

Widely known as a secondary zoonotic disease, human fascioliasis cases have increased in recent years and has become an important human disease itself (Mas-Coma et al., 1999a; Torgerson and Claxton, 1999). 2.5 million people from more than 51 countries on all five continents are affected by this liver fluke infection and 35'206 DALYs are attributed to the disease (Mas-Coma, 2005; Mas-Coma et al., 2009; Fürst et al., 2012; Cabán-Hernández et al., 2014). Another 27 million people are estimated to be at risk (Esteban et al., 1998; Cabán-Hernández et al., 2014).

In Côte d'Ivoire, less than 100 cases of human fascioliasis have been reported (Esteban 1998). Animal prevalence in the cattle-rearing northern part of the country is 12% in sheep and goat and 4% in Cattle (Achi et al., 2003a; Achi et al., 2003c). A recent slaughterhouse survey of cattle born and raised in the county has revealed that approximately 18% of all cattle livers harboured some *Fasciola gigantica* flukes (Traoré S. I. personal communication).

2.3 Biology and life cycles of schistosomiasis and fascioliasis

2.3.1 Schistosomiasis

Human schistosomiasis is caused by different species of blood flukes from the genus *Schistosoma* within the phylum *Platyhelminthes* and the class *trematodes* (Ross et al., 2002; Gryseels et al., 2006) Depending on the classification, five to seven species of medical importance are distinguished: *Schistosoma mansoni*, *Schistosoma haematobium*, *Schistosoma intercalatum*, *Schistosoma guineensis*, *Schistosoma japonicum*, *Schistosoma mekongi* and *Schistosoma malayensis* (Nithiuthai et al., 2004; Utzinger and Keiser, 2004b; Gryseels et al., 2006; Gray et al., 2011a; Weerakoon et al., 2015). The latter three species *S. mekongi*, *S. malayensis* and *S. japonicum* are grouped together into the *japonicum* species-complex (Webster et al., 2006); the same holds true for *S. intercalatum* and *S. guineensis* which likewise form a species-complex (Kane et al., 2003; Utzinger et al., 2011).

Although most human *Schistosoma* species can infect other reservoir hosts including other primates, pigs, sheep or rodents, *S. japonicum* is the only species considered to be truly zoonotic, frequently infecting other mammals of which water buffaloes play the most important role (Rollinson et al., 1987; Nithiuthai et al., 2004; Wang, 2005).

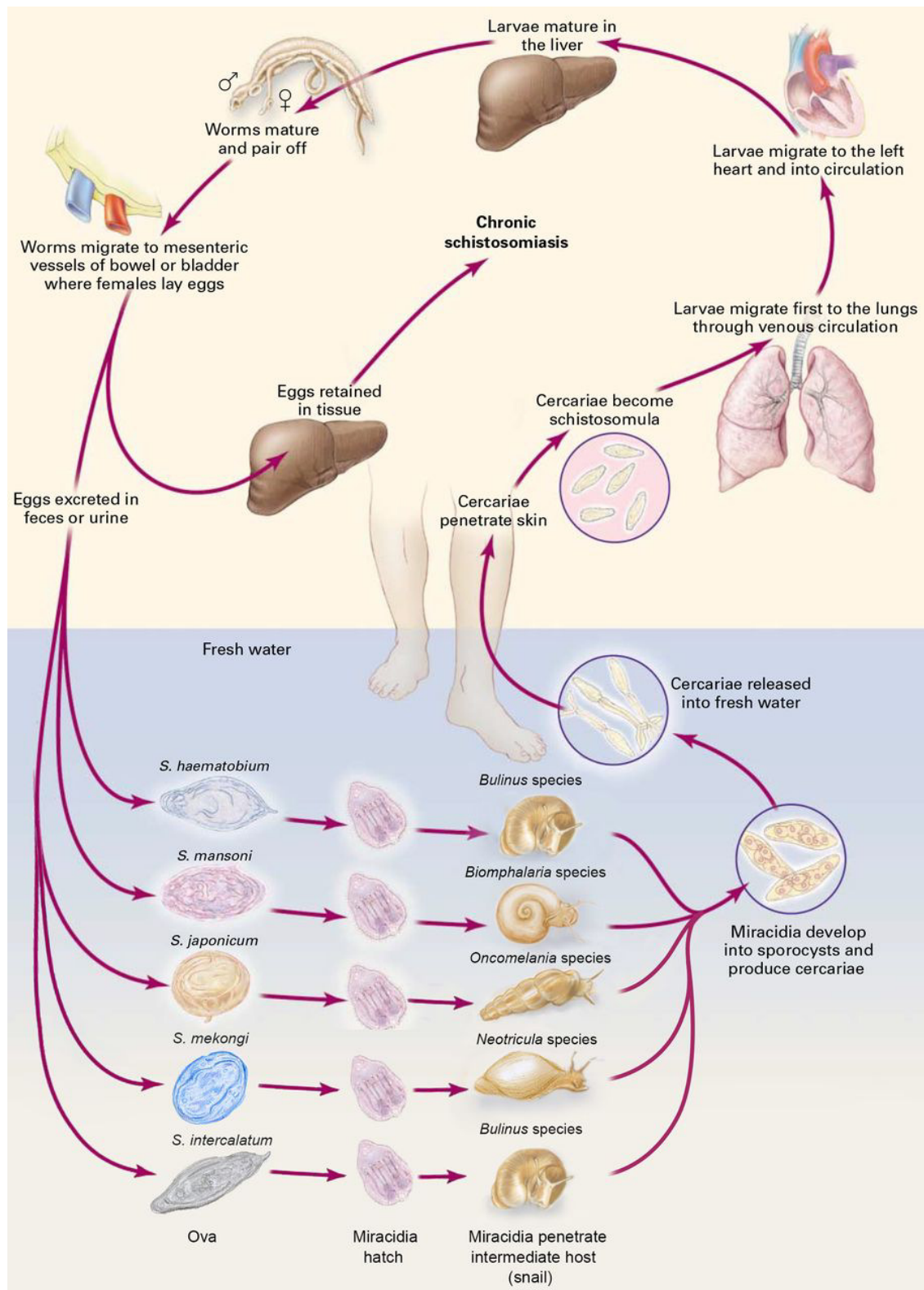
In addition to the *Schistosoma* species infecting humans as their main host, there are more than 18 *Schistosoma* species infecting other mammals or birds as final host such as *Schistosoma bovis*, *Schistosoma indicum*, *Schistosoma nasale* and *Schistosoma spindale* which are of great veterinary importance. Cercaries of other *Schistosoma* species, especially bird species, can cause cercarial dermatitis, or 'swimmers itch', in humans all over the world (Hoeffler, 1977; Nithiuthai et al., 2004; Soldánová et al., 2013).

All *Schistosoma* species are transmitted through eggs released into a suitable water body. Free-swimming miracidia hatch from the eggs and search for a suitable intermediate host snail. Within the host snail, the *Schistosoma* miracidia develops into a sporocyst producing high numbers of infectious cercaries by means of asexual

reproduction. Once asexual reproduction is completed, free-swimming, gendered cercariae are released into the water again, where they actively move to find their definitive hosts and infect them via penetration of the skin. At this point the cercaria's tail is dropped. Once within the final host, the cercariae migrate through the veins into the liver, where they mature and eventually develop into adult blood flukes. To maintain the lifecycle, the definitive host needs to be infected with at least two cercariae of the opposite sex. Within the liver, two flukes pair and the male goes on to permanently live inside the female. The schistosome-pair further migrates to the mesenteric veins of the intestine or bladder which constitutes the final home of the blood flukes. Inside these veins, the schistosomes reproduce sexually and release between 100-300 eggs per day and schistosome-pair (up to 3000 for *S. japonicum*). Eggs penetrate the epithelia of the vein and of the intestine/bladder and are subsequently excreted with the urine or stool of the host to complete the cycle (Ross et al., 2002; Roberts and Janovy, 2005; Gryseels et al., 2006; Skelly, 2008; Han et al., 2009; Gray et al., 2011b). Details of the live cycle can be seen in figure 1.3.

Intermediate host snails of Schistosoma spp.

The different *Schistosoma* species infect different intermediate host snail species. The occurrence of these snail species also determines the geographical distribution of the parasite. *S. haematobium*, *S. intercalatum* and *S. guineensis* infect snails from the *Bulinus* genus, *S. mansoni* miracidia infect snails from the *Biomphalaria* genus. *S. japonicum*, *S. mekongi* and *S. malayensis* have very specific intermediate snail host species which also explains their limited geographical distribution. *S. japonicum* is known to infect *Oncomelania hupensis hupensis*, whereas *S. mekongi* infects *Neotricula aperta* and *S. malayensis* infects *Robertsiella kaporensis* (Sturrock, 2001; Nithiuthai et al., 2004; Ohmae et al., 2004; Gryseels et al., 2006; King, 2010).



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Figure 2.3 Life cycle of *Schistosoma* spp.

2.3.2 Fascioliasis

The liver flukes from the *Fasciola* genus are also snail-borne trematodes and share large parts of their lifecycle with *Schistosoma* genus (figure 1.4). Two *Fasciola* species are responsible for fascioliasis, namely *Fasciola hepatica* and *Fasciola gigantica*. Like *Schistosoma* eggs, eggs of *Fasciola* are released into open water bodies, hatch into miracidia and infect intermediate host snails from the Family of the *Lymnaeidae* or *Planorbidae*. Within the snails, they reproduce asexually and develop into cercaries. After five to seven weeks post infection, free-swimming cercaries are being released from the snails into the open water. Other than with the *Schistosoma* genus, cercaries of *Fasciola* seek plants and encyst on them as metacercaries. When the plant is eaten by the main host, the parasite excysts and penetrates the intestine to enter into the body cavity. From there the parasite migrates through the body to the liver and finally into the bile ducts. Within the liver, it matures into an adult liver fluke and starts producing eggs which are released through the host's excreta. Alternative routes of infection are through the ingestion of cercarie-infected water, washing or irrigating vegetables with infected water or even washing kitchen utensils with infected water (Esteban et al., 1998; Esteban et al., 2002; Nithiuthai et al., 2004; Zumaquero-Ríos et al., 2013); (Mas-Coma et al., 2005)

Intermediate host snails of Fasciola spp.

Fasciola parasites infect snails from the families of the *Lymnaeidae* and *Planorbidae* mostly within the genuses *Lymnea*, *Physa*, *Galba/Fossaria*, *Radix* and *Physella* (Mandahl-Barth, 1962; Dreyfuss et al., 2002; Nithiuthai et al., 2004)

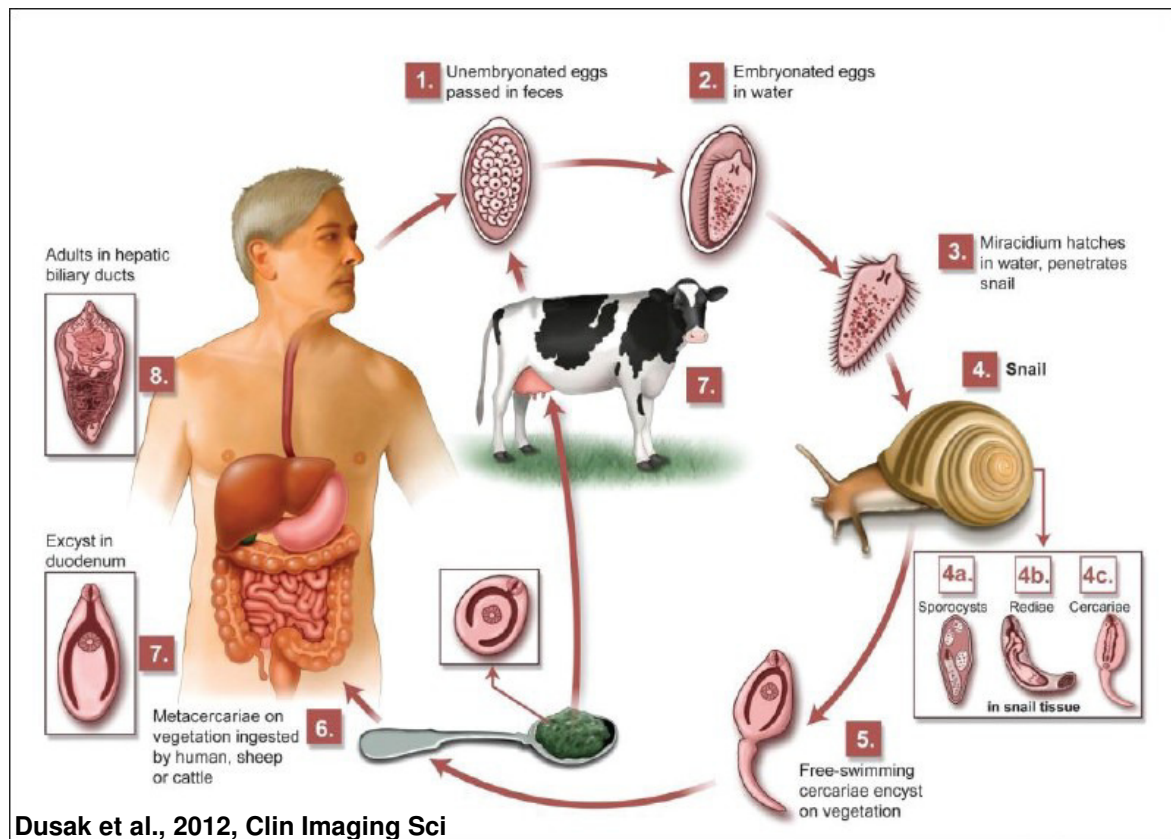


Figure 2.4. Life cycle of *Fasciola* spp.

2.4 Morbidity due to snail-borne trematodes:

Infection with snail-borne trematodes can have a wide margin of symptoms depending on the infection stage.

Schistosomiasis

During the first phase of schistosomiasis, cercarial dermatitis is a common morbidity. Although cercarial dermatitis may occur with human schistosomiasis, it is most common after infection through other *Schistosoma* species mostly infecting birds. Eggs of these species cannot differentiate in the human skin and cause a stronger immune response and inflammation. This cercarial dermatitis is most commonly known as swimmers itch (Ross et al., 2002; Nithiuthai et al., 2004).

Acute schistosomiasis is commonly known as katayama fever and occurs during the migratory phase especially in individuals from highly endemic areas who have been

hyposensitized and therefore show a stronger immune response to the deposition of eggs, symptoms include fever, headache muscle pain and belly ache in the upper right quadrant (Ross et al., 2002).

With the exception of *S. haematobium*, all *Schistosoma* species infecting humans as a final host cause intestinal schistosomiasis. Most schistosomiasis infections only show mild, unspecific symptoms and might even be perceived as asymptomatic (Hotez and Whitham, 2014), yet a plethora of morbidities are associated with chronic schistosomiasis. Pathology is mostly caused by stray eggs trapped in various tissues around the blood vessels, the bladder or intestine or various organ tissues (Brouwer et al., 2003; Andersson and Chung, 2007; Bezerra et al., 2007; Lubeya et al., 2010) Related symptoms in this phase are mostly caused by the immune response of the host, lesions and obstructions caused by the adult flukes or the eggs. Typical symptoms of the chronic infection phase in intestinal schistosomiasis, especially in heavy infections, comprise diarrhoea with occult or even visible blood or mucosa in the stool, gastro-intestinal pain, fatigue, nausea, and nutritional deficits (Ross et al., 2002; Nithiuthai et al., 2004; Vennervald and Dunne, 2004; Ajanga et al., 2006; Gryseels et al., 2006). Diarrhoea can also alternate with constipation. (Stich et al., 1999; Ross et al., 2002)

Granulomas can occur as an inflammatory response to eggs trapped in the tissue. Within the granulomas, the eggs are destroyed. However, fibrosis can occur and cause additional morbidity. The majority of these granulomas are located around the site of egg excretion in the tissue around the blood vessel, the intestine and the liver.

A more serious complication involves the formation of abscesses and unusual cell-growth which can mimic cancer. In the liver, the accumulation of granulomas and subsequent fibrosis leads to hepatosplenomegaly and portal hypertension due to the obstructions in the blood vessels (Ross et al., 2002; Nithiuthai et al., 2004). Portal hypertension can have severe consequences including hypertension and the formation of varices in the intestine or in the oesophagus. These varices can start bleeding and may cause anaemia. Bleeding in the oesophagus may even be lethal (Stich et al., 1999; Nithiuthai et al., 2004; Gryseels et al., 2006).

Interstitial pneumonitis can be caused by fibrosis in the lung, a complication more common in intestinal schistosomiasis although it has also been reported in urinary schistosomiasis (Ross et al., 2002).

Even severe morbidity is caused by the involvement of the central nervous system. Granulomas can form in the brain or spine. Cerebral schistosomiasis has a wide variety of symptoms depending on the location of the granuloma. Epilepsy has been described to be more prevalent in areas with high *Schistosoma* burden and transverse myelitis is one of the most common symptoms when the spine is involved. Meningitis is another rare manifestation of schistosomiasis involving the brain. (Ross et al., 2002; Saleem et al., 2005) In *S. haematobium*, most granulomas are found in the urogenital tract although *S. haematobium* can also cause hepatic or colonic disease (Ross et al., 2002). Eggs released into the bladder lead to dysuria and haematuria. The obstruction of the urethra and the hindrance of the urine flow from the kidneys can cause hydronephrosis – an accumulation of liquid in the kidney - and subsequently to renal colic and kidney failure (Ross et al., 2002; van der Werf et al., 2003). Calcification of the bladder wall can lead to bladder cancer (Ross et al., 2002). Mortality through *S. haematobium* arises mainly due to kidney failure and bladder cancer which is a long-term risk for urinary schistosomiasis (Nithiuthai et al., 2004; Hotez and Whitham, 2014). Secondary bacterial infections of the urinary tract are also a common pathology in urinary schistosomiasis (Ross et al., 2002)

When eggs are trapped in the genital tract, genital schistosomiasis can be the result. Trapped eggs can lead to hypertrophic cell proliferation which can become ulcerative. Genital schistosomiasis increased the risk to acquire sexually transmitted infections including HIV (Leutscher et al., 1997; Schwartz et al., 2002; King and Dangerfield-Cha, 2008; Mbabazi et al., 2011; Hotez and Whitham, 2014). Furthermore, eggs, granulomas or fibrosis in the fallopian tubes connecting the ovaries to the uterus, can lead to tubal factor infertility in women (Balasch et al., 1995; Ross et al., 2002).

Untreated *Schistosoma* infections during childhood can lead to stunting/growth retardation, anaemia, physical and cognitive impairment, memory deficits, fatigue, delayed puberty and structural deficits of the urinary tract. All these morbidities have

an impact on the later life of the child as they influence psychological and economic aspects due to reduced performance in school and work life (Ross et al., 2002; Nithiuthai et al., 2004; Vennervald and Dunne, 2004).

In pregnancy, schistosomiasis can have negative effects on the mother and the unborn child (Ross et al., 2002).

Fascioliasis

In the invasive phase, where the flukes migrate to the bile ducts and start maturing, there is a mechanical destruction of the liver tissue as well as the intestinal walls causing local allergic and toxic reaction. In this phase common symptoms include fever, abdominal pain (upper right quadrant) loss of appetite, vomiting, flatulence nausea and diarrhoea, cough, breathlessness, coughing blood and chest pain as well as urticarial rashes and eventually hepatomegaly (Nithiuthai et al., 2004; Mas-Coma et al., 2014a).

During the chronic phase, symptoms are milder and mimic those of biliary obstruction and inflammation. Morbidity in the chronic phase is caused by adult flukes and the deposition of eggs causing inflammation as well as unusual cell proliferation in the epithelium and thickening of the bile duct and gallbladder walls. Inflammation of the bile ducts and the gall bladder lead to obstructions which can cause severe pain, hepatomegaly, fever, biliary colic, fatty food intolerance, nausea, and jaundice. Bleeding and venous thrombosis have also been reported along with pancreatitis in long-term chronic infections (Nithiuthai et al., 2004; Ashrafi et al., 2014).

Ectopic fascioliasis can occur and cause symptoms when flukes or eggs are located outside of the liver and bile ducts. Symptoms range from obstructions in the oesophageal mucosa to ocular and even cerebral fascioliasis (Mas-Coma et al., 2014a). Fibrosis occurs most commonly in the gastrointestinal tract, the pancreas, spleen, heart, blood vessels, lung, muscles and the. The brain and the eye can also be involved in rare cases causing a wide array of neurological symptoms (Nithiuthai et al., 2004; Ashrafi et al., 2014).

2.5 Diagnostics

The standard method for the diagnosis of intestinal schistosomiasis is the Kato Katz thick smear using 42 mg templates which allows for a quantification of egg excretion and thus infection intensities (Kato and Miura, 1954; Katz et al., 1972a; Montresor et al., 1998). Due to the day to day and intra specimen variations in egg counts/ egg excretion, it has been suggested to test multiple samples over consecutive days (Nielsen and Mojon, 1987; Utzinger et al., 2001a; Booth et al., 2003a; Booth et al., 2003b; Steinmann et al., 2007; Knopp et al., 2008). Homogenizing whole-stool samples or smaller stool pieces prior to diagnosis has also been shown to deliver more reliable estimations of infection intensities (Krauth et al., 2012).

Urinary schistosomiasis is commonly diagnosed with the filtration of 10 ml of homogenized urine pressed through a 13 mm diameter Nyltel filter with a mesh size of 20 µm filter and with subsequent Lugol staining and examination under a microscope (Mott et al., 1982; Savioli et al., 1990b)

Questionnaires on self-reported symptoms can be used for the rapid identification of high-risk populations (Mafe et al., 2000; Utzinger et al., 2000; Lengeler et al., 2002a; Raso et al., 2004; Bassiouny et al., 2014). The usefulness of this rapid assessment has been often evaluated in sub Saharan Africa. However, it has been shown that the performance of questionnaire assessment is less good for *S. mansoni* infections, especially in light infections (Brooker et al., 2009)

Reagent strip testing for microhaematuria as a proxy for *S. haematobium* has been proven to perform well and have good sensitivity and specificity (Bogoch et al., 2012; King and Bertsch, 2013; Ochodo et al., 2015).

In developed countries, ultrasound can be used to effectively diagnose chronic/established schistosomiasis and associated morbidity. Yet this diagnostic method is most useful in a hospital setting whereas it is not feasible as a tool in research or community assessment of infections (Hatz, 2001; Richter et al., 2003).

Immunodiagnostic methods can overcome some of the practical limitations of direct laboratory testing of schistosomiasis (Van Lieshout et al., 2000; Obeng et al., 2008). One of the most promising newly developed diagnostic tools for intestinal schistosomiasis is the Point-of-care circulating cathodic antigen (*POC-CCA*) test.

The principle of the *POC-CCA* is based on the lateral-flow of a urine sample using a nitrocellulose strip covered with anti-CCA monoclonal antibodies (Van Lieshout et al., 2000; Van Dam et al., 2004a). *POC-CCA* test cassettes are especially useful in resource constrained settings where a trained laboratory technician, a microscope and/or electricity is not available (Stothard et al., 2009b; Coulibaly et al., 2013b)

PCR can also be employed for diagnosis and quantification of *S. mansoni* and *S. haematobium*. Real time PCR had high sensitivity for the diagnosis of *S. haematobium* compared to urine filtration and CCA test (Obeng et al., 2008). However, this method is highly complicated and resource intensive and thus not suitable in a fieldwork setting (Pontes et al., 2002; Robert et al., 2008; Gomes et al., 2014). Metabolic profiling is also a method requiring extensive resources and knowledge and which is therefore more suitable for developed countries (Holmes, 2010; Wang et al., 2010).

When morbidity control is the main issue at hand, direct methods perform well. Especially because high intensity infections are easier to detected. However, after treatment of in low-prevalence settings better, more sensitive and specific diagnostic tools are urgently needed (Bergquist et al., 2009; Gomes et al., 2014; Utzinger et al., 2015).

Despite on-going research, there still is no highly specific and sensitive method for the diagnosis of *F. hepatica* or *F. gigantica* infection and the differentiation of pre-patent from patent infection (Rojas et al., 2014).

So far, the diagnosis of human fascioliasis is mostly done through the detection of eggs in faeces for example with the Kato Katz thick smear or sedimentation techniques However the passing of eggs in fascioliasis only occurs in the chronic phase and is quite irregular. Therefore, the examination of up to six stool samples is often necessary. (Cabán-Hernández et al., 2014).

Some Immuno-diagnostic methods, such as enzyme-linked immunosorbent assays (ELISA) for the diagnosis of fascioliasis have been developed which allow for high sensitivity and enables diagnostics even in the acute phase where no eggs are being excreted. Recent developments incorporate the ELISA method into rapid diagnostic lateral flow devices. However, Antibody testing entails the disadvantage

of being unable to distinguish past infections or exposure from current infections (Rojas et al., 2014). As with the diagnosis of schistosomiasis, highly elaborate molecular methods can be employed but are not feasible for the diagnosis in resource-constrained settings. The Loop-mediated isothermal amplification (LAMP) method circumvents some of the shortcomings of molecular methods through enabling the amplification of DNA at a constant temperature, eliminate the need for expensive thermocycler usually needed for DNA replication. Nevertheless, this method still needs some elaborate technologies and a laboratory (Ai et al., 2010).

The WHO highlighted the need for diagnostic techniques which more accurate than the ones traditionally used for the diagnosis of human fascioliasis (Chen and Mott, 1990; Nithiuthai et al., 2004; Cabada and White, 2012; Mas-Coma et al., 2014b).

2.6 Treatment and control

The current control strategy proposed by the World Health Organization (WHO) and the World Health assembly is preventive chemotherapy aiming at reducing the burden due to schistosomiasis. Since the 54th world health assembly, where it was proposed to treat at least 75% of at-risk children, many national control programmes have been launched in endemic countries (WHO, 2002b; Kabatereine et al., 2006; Hotez et al., 2007). Treatment plans depend on the underlying prevalence in the area (table 1.1). Drug administration is mostly performed without prior treatment since Praziquantel is considered safe and diagnostic tools are not always reliable (Woolhouse, 1998; WHO, 2002b; Fenwick et al., 2003; Albonico et al., 2006; Fenwick and Webster, 2006; Anderson et al., 2013).

Table 2.1 Treatment plan for schistosomiasis control in school-aged children (adapted from WHO, 2006, 2011)

Category	Prevalence	Treatment plan
<i>Schistosomiasis</i>		
High-risk area	≥ 50%	Treatment of all school-aged children including the ones not enrolled in school as well as at-risk adults once a year
Moderate-risk area	≥ 10% and < 50%	< Treatment of all school-aged children including the ones not enrolled in school as well as at-risk adults every two years
Low-risk area	≥ 1% and < 10%	Treat all school aged children when they enter school and again when they leave school and treat suspected cases at hospitals and health centres

The treatment of choice against schistosomiasis is Praziquantel at a dose of 40mg/Kg body weight (WHO, 2002b; Fenwick et al., 2003; Utzinger and Keiser, 2004b; Doenhoff et al., 2008). Praziquantel is considered to be a safe drug with a broad spectrum of efficiency against many *Schistosoma* species (Fenwick et al., 2003; Utzinger and Keiser, 2004b; Doenhoff et al., 2008; Cioli et al., 2014). However, Praziquantel is comparatively expensive when compared to other anthelmintic drugs and it is not being produced in sufficient quantities to treat everyone in need (Hotez et al., 2010; WHO, 2013a). The number of Praziquantel tablets needed per year to treat all school-aged children is estimated to be between 121 and 125 million. for community based treatment this number would raise to 239 million to 256 million (Lai et al., 2015). Furthermore, Praziquantel lacks efficacy against juvenile *Schistosoma* flukes (Hotez et al., 2010; WHO, 2013a). Other active compounds against schistosomiasis include Oxaminiquine against *S. mansoni* and Metrifonate against *S. haematobium*. (Feldmeier and Chitsulo, 1999; Thiongo et al., 2002; Fenwick and Webster, 2006; Utzinger et al., 2011). Artemisininins have shown

efficacy against juvenile schistosomes.(Shuhua et al., 2002; Utzinger et al., 2007). some efforts have been made to investigate the usefulness of combination therapies to achieve better cure rates (Keiser and Utzinger, 2007; Utzinger et al., 2007). Additionally possibilities to develop a vaccine are investigated alongside the discovery of new drugs (Keiser and Utzinger, 2007)

Apart from mass drug administration, other factors play a role in the effective control of schistosomiasis. Although the efforts are comparatively small, some try to improve safe-water supply to reduce exposure as well as the building of adequate sanitation facilities alongside health education to interrupt the contamination of open water with schistosomiasis (Useh and Ejezie, 1999; Asaolu and Ofoezie, 2003; Stothard et al., 2009a; Utzinger et al., 2009a; Rollinson et al., 2013b; Grimes et al., 2015).

Snail control is another issue that would also benefit the fight against fascioliasis as it would reduce the number of intermediate hosts for the parasite. So far, only a few countries have integrated snail control in the fight against schistosomiasis. Chemical snail control measures are not always accepted by the population because the Niclosamide – the chemical most commonly used for snail control, also kills other water organisms including fish (Takougang et al., 2007; WHO, 2013b). Despite all difficulties, great advances have been made in the last few decades and it has now been suggested that elimination of schistosomiasis should be attempted as a next step in the fight against schistosomiasis (WHO, 2012a; Rollinson et al., 2013b).

No large-scale control programmes against human fascioliasis exist. Treatment of human fascioliasis is done with Triclabendazole as the drug of choice. Nitazoyanide can be used in the chronic phase of fascioliasis as an alternative drug (WHO, 2008; Zumaquero-Ríos et al., 2013).

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Introduction

Zumaquero-Ríos, J.L., Sarracent-Pérez, J., Rojas-García, R., Rojas-Rivero, L., Martínez-Tovilla, Y., Valero, M.A., Mas-Coma, S., 2013. Fascioliasis and Intestinal Parasitoses Affecting Schoolchildren in Atlixco, Puebla State, Mexico: Epidemiology and Treatment with Nitazoxanide. *PLoS Negl Trop Dis* 7, e2553.

3. Goals and specific objectives

The overarching goal of this work was to obtain a systems overview of schistosomiasis and fascioliasis in the northern area of Côte d'Ivoire paying attention to disease prevalence, social and ecological factors (including behaviours, access to water and sanitation and cultural determinants) as well as methodological considerations.

3.1 Specific objectives

Specific objectives of this PhD Thesis include:

- To review, summarize and evaluate existing household sampling methods for epidemiological studies and propose a sampling frame for researchers and other field worker.
- To evaluate currently existing rapid diagnostic tools for the assessment of schistosomiasis infection within communities.
- To elucidate prevailing water contact patterns and underlying reasons thereof leading to an increased exposure to schistosomiasis and fascioliasis for the local communities in northern Côte d'Ivoire
- To assess the distribution and ecological determinants of aquatic snail species serving as intermediate hosts for schistosomiasis and fascioliasis and relating it to prevailing prevalence of infections within the human communities using these water sources.

4. Study sites, survey design and sample size

Fieldwork for this thesis was conducted in the District des Savanes, northern Côte d'Ivoire. The northern part of Côte d'Ivoire is characterised by a semi-arid Sudano-Guinean climate with a distinct rainy season from June to October and an annual precipitation of 800 to 1400mm (FAO, 2009). The dry season lasts from November to May and is marked by the Harmattan, a hot and dry wind from the Sahara. This Harmattan period is marked by cold nights, hot days and very low humidity and is followed by an upsurge in temperature from the end of February to mid-March. The mean temperature is 25°C during the rainy season and 28°C during the dry season (Aka et al., 2000). The ecology is characterised by mostly semi-arid soil interspersed by many small rivers flowing from North to South, small water bodies that often drain during dry season and small water reservoirs (Dams) that have been constructed since in the 1970s to promote and further develop livestock farming and agriculture (Cecchi, 1998). The region of Tchologo, with its capital Ferkessédougou, is part of the District des Savanes and is situated between 8.615252° and 10.465472°N latitude and 3.806663° and 5.984530° W longitude, with a total surface of 17'728 km². To the north and east, it shares borders with Mali and Burkina Faso. The prevailing ethnic groups of the study area are the Senoufo and members of the semi-nomadic Peulh population, also known as Fulani.

For the rapid assessment of infection with schistosomiasis, teachers of the class CE2 (4th grade) of 100 primary schools randomly selected based on a complete list of all 571 public, private and confessional schools in the administrative region of Tchologo within the District des Savanes were invited for a one-day training on performing questionnaire surveys and rapid diagnostic tests. All schools received a rapid-assessment questionnaire as well as 30 reagent strip tests for microhaematuria. An additional 20 schools received a box of 25 point of care circulating cathodic antigen test (*POC-CCA*) cassette for the rapid assessment of *Schistosoma mansoni* infection. Teachers were asked to perform all tests they received with 30 randomly selected children of class CE2. If there weren't enough children in class CE2, teachers were asked to complement the sample, first, with

children from class CE1 (3rd grade) and then with children from class CM1 (5th grade). For quality control, questionnaire surveys and rapid diagnostic tests were performed by the author of this doctoral thesis herself in 5 of the invited 100 schools.

In total 56 teachers followed the invitation and received the questionnaires and rapid assessment tests. By the end of the school year, 40 schools had returned results and in five schools the field team had generated the results.

For the fieldwork pertaining to the access to, and use of, water sources in the District des Savannes, 10 villages were randomly selected on the basis of a list of all primary schools in the entire District des Savanes. Further details on the selection procedure as well as study methodologies for this survey can be found in Chapter 7.

For the main bulk of fieldwork, 30 villages in the region de Tchologo, in the District des Savanes were selected using a multi-stage semi-random cluster sampling approach based on the prior results of the baseline survey of this work as well as the baseline survey performed in the frame of the PhD thesis of Dr. vet. Seïdinan Ibrahima Traoré within the same umbrella project. For this sampling, a list with all 231 villages in the Tchologo region was obtained from the district authorities. 72 villages with information available from the baseline surveys (on human infection with schistosomiasis or on animal infection with fascioliasis) were added into a first list. All 159 villages with no data available were put into a second list. Thus the first list contained 72 villages with available infection data and the second list contained 159 villages without infection data. In a next step, 28 villages from the first list and 2 villages from the second list villages were randomly selected. The chance of a village to be selected from the first list was 12% ($72/231 = 31.2\%$ [~chance of being selected originally] times $28/72 = 38.9\%$ [chance of being selected from List 1]). The chance of being selected from the second list was 1.3% ($2/159$). Thus all villages had an equal chance of being included in the baseline surveys but for the follow-up survey, villages with data from the baseline surveys had a higher chance of being in the sample than villages with no data available.

Around each of the selected villages, one to two small Peulh settlements were identified with the help of village authorities and included in the survey as well. These Peulh settlements were counted to the same cluster (village).

Within each village, study subjects were selected using an adapted version of the sampling method from the extended programme of immunization (EPI).

Details on the method used for the study can be found in Chapter 4 under the name **Krauth1 (W20)**. In short, from a central point in the village, five investigators chose a random direction by turning a pen. Each investigator was equipped with a package of lots including numbers from 1 to 20. Household selection was performed by drawing a random number and selecting the x^{th} household in this direction according to the number drawn. If no eligible person was found in the household, the nearest household in the same direction was selected instead until an eligible person was found. From the last included household a new number from the full package of lots was drawn. The investigators continued in this manner until the total sample of the respective survey was achieved or no more eligible subjects were available in the cluster. At times the majority of village inhabitants were working on the field. In this case one or several of the investigators went to the respective field and randomly selected a number of participants at this location.



Figure 4.1 Study area

Rose: district des Savanes; dark rose: region de Tchologo;
Blue: study sites region de Tchologo; Orange: study sites in the district des Savanes.

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5. A guide to household sampling in the field: computer-simulated comparison of existing methods and review of the literature

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5.1 Abstract

Background: The decision which sampling method to employ for a study greatly influences the usefulness and interpretation of acquired data. To obtain a sample representative of the study population a random sampling has to be employed. However, random sampling is not always feasible in resource constrained settings where sampling frames are sometimes non-existent and would be impossible to create. Alternative sampling methods have been proposed by various authors, the most well-known is a spatial approach by the Extended Programme of. The aim of this work was to review and summarize existing household sampling methods and evaluate their performance using computer simulation on a real village outline.

Methods: A systematic literature review was performed to identify existing household sampling methods. Identified methods which relied on a spatial approach where then simulated using Python. The resulting samples where then evaluated and compared in their performance on oversampling, systematic exclusion of households and the amount of clustering within the samples. A decision frame for identifying suitable household sampling method is put forward.

Results: compared to random sampling, all spatial methods greatly oversampled households around the starting point of the method. The original EPI method as well as several adaptations thereof produced poor samples irrespective of the underlying probability of finding an eligible subject in a household. High numbers of households in the village were systematically excluded and clustering was high. One household sampling method proposed here for the first time achieved significantly better samples compared to existing spatial approaches. Nevertheless, it also slightly oversamples households around the start point. However, of greater importance is that with only 4 houses, it excludes considerably less households compared to any other method apart from random sampling.

Conclusion: Where possible, random sampling should be used and sampling frames can be created or updated using approaches proposed by different authors. Only where this is not possible a spatial sampling method could be employed. Of all tested methods, the Krauth 3 (W20+1) method produced the most promising result.

5.2 Introduction

Only a handful of techniques are available for household sampling in low-resource setting (Henderson and Sundaresan, 1982a). The paucity of sampling frames and techniques is surprising, particularly in view of the potential influence on outcomes of any survey (Fowler, 2013; Levy and Lemeshow, 2013). Yet, in theory, proper sample selection has therefore been widely discussed, covering all aspects from sample size, definition of study population and sampling strategies, much of which is textbook knowledge (Fowler, 2013; Levy and Lemeshow, 2013). Indeed, there is a wide variety of sampling methods, ranging from purposive to random sampling, depending on the scope of the project and the research questions at hand. But while the theories are well known and understood, researchers face a myriad of challenges when implementing the chosen sampling method under real-life field conditions (Bennett et al., 1994; Bostoen and Chalabi, 2006; Vanden Eng et al., 2007; Winkler et al., 2010). For example, a simple random sampling is much more difficult in practice than in theory. All eligible subjects have to be identified and listed. Once selected, the individual has to be identified and located. Furthermore, “random” selection which is performed with the aid of a computer programme is rarely truly random, as acknowledged for some widely used random-number generators within Microsoft Excel, Visual Basic and Java (L'Ecuyer, 2001; McCullough and Heiser, 2008).

Arriving at a sample of clusters/villages from a predefined country or another administrative unit is mostly straightforward, since information up to this level is often readily available (Murthy, 1981). However, once the selection of individuals or households has to be performed, there are many practical challenges rendering the correct implementation of the theoretical principles difficult. A complete list of persons or even of household addresses is rarely available and is hard to obtain even in high-income countries, let alone low- and middle-income countries. Moreover, available lists are soon out of date (Woolsey, 1956). Furthermore, informal or illegal settlements within a cluster are not represented on official lists,

and hence will be excluded from the sample (Vanden Eng et al., 2007; Alves et al., 2011).

Some alternative methods have been proposed to achieve a representative sample of households or individuals within a cluster in the absence of a complete registry and a lack of resources to create such a registry. A widely known method stems from the extended programme of immunization (EPI) of the World Health Organization (WHO) which was invented in order to allow the programme to estimate vaccination coverage in developing countries (Woolsey, 1956; Agadzi, 1978; Henderson and Sundaresan, 1982a). Over the last three decades, several adaptations have been made their feasibility validated in different settings (Bennett et al., 1994; Turner et al., 1996; Winkler et al., 2010; Sollom et al., 2011). Additionally, some methods have been introduced for more specific requirements, such as sampling within rapidly changing communities like slums and sampling for the rapid assessment of coverage (Bennett et al., 1994; Hoshaw-Woodard, 2001; Alves et al., 2011). The EPI and other methods have well-known disadvantages over simple random sampling, and hence a random sample is still the go-to method of choice (Anker, 1991; Bennett et al., 1991; Bostoen and Chalabi, 2006). However, sometimes situations on the ground render a random sampling unfeasible, unless one has the resources to invest large amounts of time and money for the creation of sampling frames down to the level of the individual.

We therefore aim to summarise published and newly proposed household sampling methods and test their performance with the goal to identify the one most suitable to provide a good sample close to the features of a random sampling while at the same time being easily implementable in a field settings with all its limitations.

Specific objectives include

- 1) To identify published methods of household sampling for epidemiological studies
- 2) To evaluate and compare the identified sampling methods and identify the ones producing results most closely to random sampling
- 3) To create a decision frame for researchers and field worker to identify the household sampling method most suitable to their research question

5.3 Materials and methods

5.3.1 Ethics statement

Four out of five villages used for simulation purposes are villages selected for a study pertaining to access to, and use of, water sources by people (and livestock) from the district des Savanes in northern Côte d'Ivoire (Krauth et al., 2015a). Ethical clearance was granted by the ethics committees of Basel (reference no. EKBB 64/13) and Côte d'Ivoire (reference no. 32-MSLS/CNERdkn). Regional and local authorities gave their consent for these villages to be part of the study. Participants from households selected during the study provided written informed consent. The fifth village is a Swiss village of which the outlines were retrieved online from Google Earth. No actual sampling took place in the Swiss village, and hence, no ethical clearance was necessary.

5.3.2 Systematic review

A systematic review was performed to identify publications about household sampling methods employing scientific studies. We searched PubMed (from inception to 30 July 2015), using the following search terms: (i) household sampling and (ii) household sample, without any language restrictions. Publications were retrieved in an EndNote database.

The titles and abstracts of the obtained list of publications were screened for relevant manuscripts which describe a household sampling method or propose an alteration of an already established method. Additionally, the references of relevant publications were screened for potential further articles that might not have turned up in the prior PubMed search. All articles describing a household sampling method or an adaptation thereof –mentioned for the first time – were included in the final list of publications. Only methods describing sampling methods within a cluster or village were included.

5.3.3 Selected villages for simulation

Satellite images of five villages, four from the district des Savanes in northern Côte d'Ivoire and one from Basel-Landschaft, Switzerland, were retrieved from Google

Earth. All visible buildings on these images were hand-marked with a dot by the first author, using Gimp 2.8.2[©] (1995-2012 Spencer Kimball, Peter Mattis and the GIMP Development Team). Village outlines and a distance scale were included in the image. The created files were read into Python version 2.7.10[©] (2001-2015, Python Software Foundation) for simulation of the different household sampling methods.

5.3.4 Simulations

Household sampling methods eligible for simulation (i.e. sampling methods that did not include prior mapping of the village for subsequent random sampling or multi-stage cluster sampling) were scripted using Python. All sampling methods were iterated 1000 times with five players (investigators) per iteration in five different village outlines. Additionally, all sampling methods were performed with different likelihoods (from 30% – 95%) to find an eligible person in the household to simulate differences in the inclusion criteria.

5.3.5 Statistical analysis

Histograms were created depicting how many households of a given village were sampled how often by each method. Additionally, frequency-distribution maps of all samplings within each village were created. Furthermore, a point-pattern analysis was conducted to compute the amount of clustering within each sample. For this point-pattern analysis a grid with the size of A/n , where A depicts the area of the village and n is the sample size, was put over the village. The mean number of sampled houses within the squares as well as the variance was calculated. The ratio of variance/mean gives an indication of clustering, whereas 0 equals uniform distribution, 1 equals random distribution and >1 equals clustered distribution. Subsequently the average variance/mean ratio over all iterations is calculated to generate the average clustering for each sampling method. Of note, for the purpose of this manuscript, we are taking houses as a proxy for households, well aware that the definition and selection of households within the houses and the selection of individuals within the households is not trivial due to difficulties in defining a “household” and in explaining to other household members why one individual was chosen but not the other (Leone et al., 2010).

5.4 Results

5.4.1 Systematic review

A total of 1,236 hits were identified on PubMed of which 136 were duplicates. Of the remaining 1,100, 15 manuscripts described a specific method for household sampling, that are briefly summarized below. Of note, for the description of the methods, initial random selection of the clusters in which each method is being performed is presumed.

5.4.2 Simulatable sampling methods

EPI: (Henderson and Sundaresan, 1982a) **Description:** Select one house randomly as starting point and investigate for individuals of the appropriate inclusion criteria. Continue with the house nearest to the last house and investigate likewise. Continue until the required number of subjects fulfilling inclusion criteria is sampled. All individuals of the appropriate inclusion criteria living in the last household falling into the sample are included even if this means including eight to ten individuals, instead of the proposed seven.

EPI D/2: (Sollom et al., 2011) **Description:** Walk the diameter of the village and count all houses in the road (D). At the centre of the village select a random direction. Draw a random number between one and $D/2$ and chose this house as starting point. Then continue in EPI fashion.

Winkler: (Winkler et al., 2010) **Description:** At the centre of the cluster/village, randomly select two to three directions by spinning a bottle. Walk in the selected directions as well as perpendicular to them until the edge of the cluster and count all houses. For each of the resulting four to six directions, the start point is determined by randomly drawing a number between one and x_d (where x equals the number of houses in the direction d). From these starting points, the EPI method is performed all selected directions until the required number of houses are included.

EPI spin again: (Bennett et al., 1994) *Description:* Like EPI but chose random direction again at each sampled house and take closest house in this direction for next investigation.

EPI3: (Bennett et al., 1994) *Description:* Like EPI but spin bottle again at last sampled house and take the third nearest household.

EPI5: (Bennett et al., 1994) *Description:* Like EPI but spin bottle again at last sampled and take the fifth nearest household

Peri: (Bennett et al., 1994) *Description:* spin bottle to select random direction from centre of the cluster. Choose first house in this direction and do EPI from there. Select half of the required number of individuals. Return to centre, spin bottle again, choose last house in that direction and start EPI from there.

QTR: (Bennett et al., 1994) *Description:* Divide the village into four quadrants. Perform EPI sampling in each of the four quadrants by sampling $\frac{1}{4}$ of the total sample in each quadrant.

Systematic: (unpublished) *Description:* Select five random directions from the centre of the cluster. Count all houses in these directions until the border of the cluster. Divide the number of houses by the number of samples needed in each direction (x). Return to the centre and sample each x^{th} house in this direction. If no eligible person is found in this house, sample the next nearest house (and continue counting from there).

Systematic with random start: (unpublished) *Description:* Select five random directions from the centre of the cluster. Count all houses in these directions until the border of the cluster. Divide the number of houses by the number of samples needed in each direction (x). Return to the centre and select a random house between one and x as starting point. From this starting house sample each x^{th} house in this direction. If no eligible person is found in this house, sample the next nearest house.

Krauth1 (W20): (Krauth et al., 2015b) *Description:* (Using five investigators or repeat five times) Choose random direction from centre of the village. Draw a random number x between one and 20 and take the resulting x^{th} house as starting

point. Using a dice or pouch of lots, raw random number between one and 20 again after each included household. If no eligible subjects are in the house, take the nearest in the same direction. Once arriving at the border of the village continue backwards in the same direction. Each investigator samples one fifth of the total sample.

Krauth2 (W20+1): (Unpublished) *Description:* Like Krauth 1 but include a 21st side to the dice/ a 21st lot indicating that the investigator needs to randomly selection a new direction.

Krauth3 (W(R/#)): (Unpublished) *Description:* Like Krauth 1 but count all houses in the selected direction (*R*) and determine size of dice/number of lots by *R/#* (where # equals number of households required from this direction).

5.4.3 Variations of cluster sampling

Compact segment sampling: (Turner et al., 1996; Milligan et al., 2004; Alves et al., 2011) *Description:* Sketch map entire cluster/village, divide into approximately equally sized sub-clusters (e.g. # of required samples), select one cluster at random and include all households in the selected segment.

Multiple compact segment sampling: (Hoshaw-Woodard, 2001) *Description:* Sketch map entire cluster/village, divide into approximately equally sized sub-clusters. Select several segments in each cluster and sample households in each cluster.

Multi-stage cluster sample and random selection of clusters: (Hoshaw-Woodard, 2001) *Description:* Divide cluster/village in several segments. Sample segments proportional to size and draw a random sample of households within each selected segment (needs to obtain/create list of households per selected segment).

5.4.4 Methods to obtain and update a list of households for random sampling

National statistics: (Murthy, 1981) *Description:* For each survey in any country, create a master-sampling frame pertaining to administrative divisions of all

hierarchical levels. Perform a random sample of each of the primary sampling unit, secondary sampling units and ultimate sampling units (cluster sampling).

GPS assisted random sampling: (Vanden Eng et al., 2007) **Description:** Geo-reference all houses in the cluster using several investigators with tablet computers. Draw a random sample of coordinates from the obtained list and use the tablet computer to find the house again.

Woolse: (Woolsey, 1956) **Description:** start with a list of blocks/segments of the cluster (obtained from authorities or prior surveys). Select a random sample of segments. Visit these segments and enter any new address into the list. Additionally, identify areas of recent construction and enter all addresses from these areas into the list. Then draw a random sample from the thus created new list of addresses.

5.4.5 Further sampling methods for specific requirements

LQAS: (Lot quality assurance sampling) (Hoshaw-Woodard, 2001) Suitable for assessment of whether a certain threshold (binary variable) value is achieved or not (vaccination coverage, reach of intervention, etc.). Not quantitative. **Description:** The population is divided into segments and a random sample is drawn in each segment. The proportion of the desired parameter is assessed in each segment then the overall proportion for the survey area is calculated by combining the weighted proportions of all segments.

Double sampling: (Hoshaw-Woodard, 2001) Suitable for assessment of whether a certain threshold (binary variable) value is achieved or not (vaccination coverage, reach of intervention etc.). Not quantitative. **Description:** A first sample n_1 is drawn for each segment. If the desired threshold is reached after this, the sampling is over and the segment is classified as “threshold achieved”. If the threshold is not achieved, another sample n_2 is selected within the same segment. If the threshold is achieved by combining n_1 and n_2 then the whole lot is classified as “threshold achieved” otherwise as “threshold not achieved”.

Stratified sampling by specific groups: (Hoshaw-Woodard, 2001) Suitable for surveys seeking to compare outcomes between different population groups.

Description: Divide the population into non-overlapping population groups of interest (e.g. by age, ethnicity or socio-economic quintile). A random sample is taken from every stratum. This ensures inclusion of members even from very small population groups.

5.4.6 Comparison of simulated sampling methods

Note: the following results are preliminary results from a reduced computation of only 250 iterations of 10 methods (random, systematic, EPI, EPI3; EPI5; EPI D/2, EPI spin again and Krauth 1, 2 and 3) at a reduced set of chances to meet inclusion criteria of 30%, 50%, 70% and 95% in one of the villages.

From the histograms it can be seen that with a 30% chance to find an eligible subject in a household, none of the simulated sampling methods performed to the standards of the simple random sample. Most methods clearly oversample the area around the starting point where the random directions are chosen. Also, the vast majority of methods show a high number of systematically excluded households throughout all 250 iterations. Especially the **EPI spin again** and **EPI D/2** excluded very high numbers of households with 108 and 122, respectively for a 30% chance of meeting inclusion criteria (figure 4.1) and 187 and 178, respectively for a 95% chance of meeting inclusion criteria. The fewest households were excluded by **Krauth2 (W20+1)**.

Oversampling was smallest in the **EPI5** and **EPI3** method as well as with the **Krauth2 (W20+1)** (figures 4.1 and 4.3) and most prominent with **EPI spin again**, **EPI D/2** and **Krauth 1 (W20)**.

When the chance to find an eligible subject in a household was increased to 95%, the overall picture shows the same trend but with more extreme magnitudes. The methods **EPI spin again** and **EPI D/2** exclude 123 and 118 households, respectively. The number of excluded households at a 95% chance of including a sampled household also increased for most other methods with only two exceptions, the **EPI** method which excluded marginally less households (~28 instead of ~37) and the **Krauth2 (W20+1)** which excluded only two instead of four households.

Oversampling of certain households also becomes much more pronounced with some houses being included in up to 197 out of 250 iteration.

Figures 4.3 to 4.6 depict the frequency of inclusion over all iterations for **EPI spin again** (performing worst) and **Krauth2 (W20+1)** (performing best). It can be seen that the centre of the village is mostly being oversampled and the outskirts of the village is less frequently sampled. However, some methods perform better than other in reaching all houses with the same likelihood and indeed the **Krauth2 (W20+1)** works best in terms of excluded houses and oversampled houses. Figure 4.5 shows households actually included during a survey in the pictured village with the **Krauth1 (W20)** approach as well as the map of frequency-distribution from the simulation.

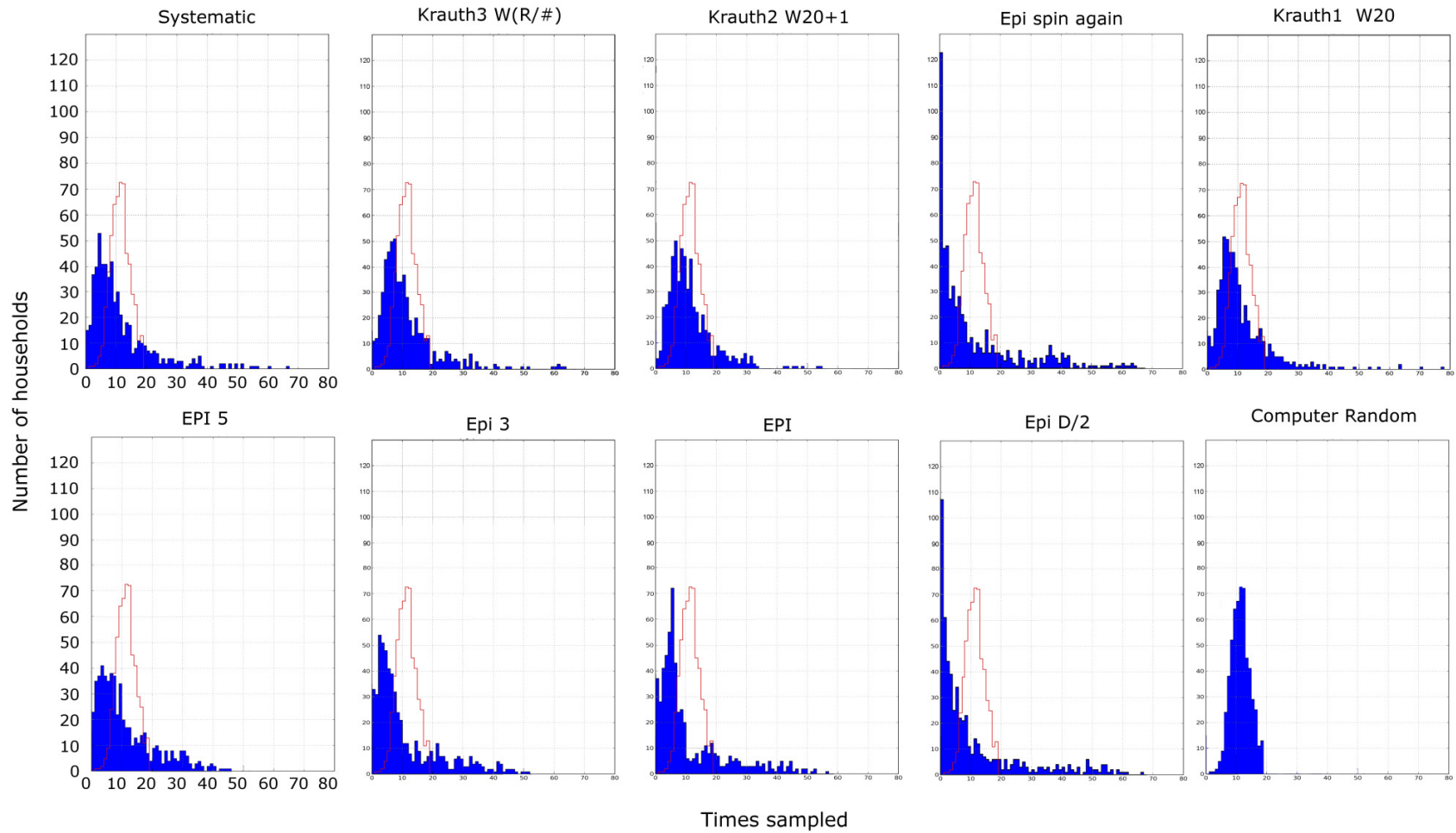


Figure 5.1 Histograms of household inclusion frequency per simulated method at 30% chance of meeting inclusion criteria.

Red, outline from the random sampling

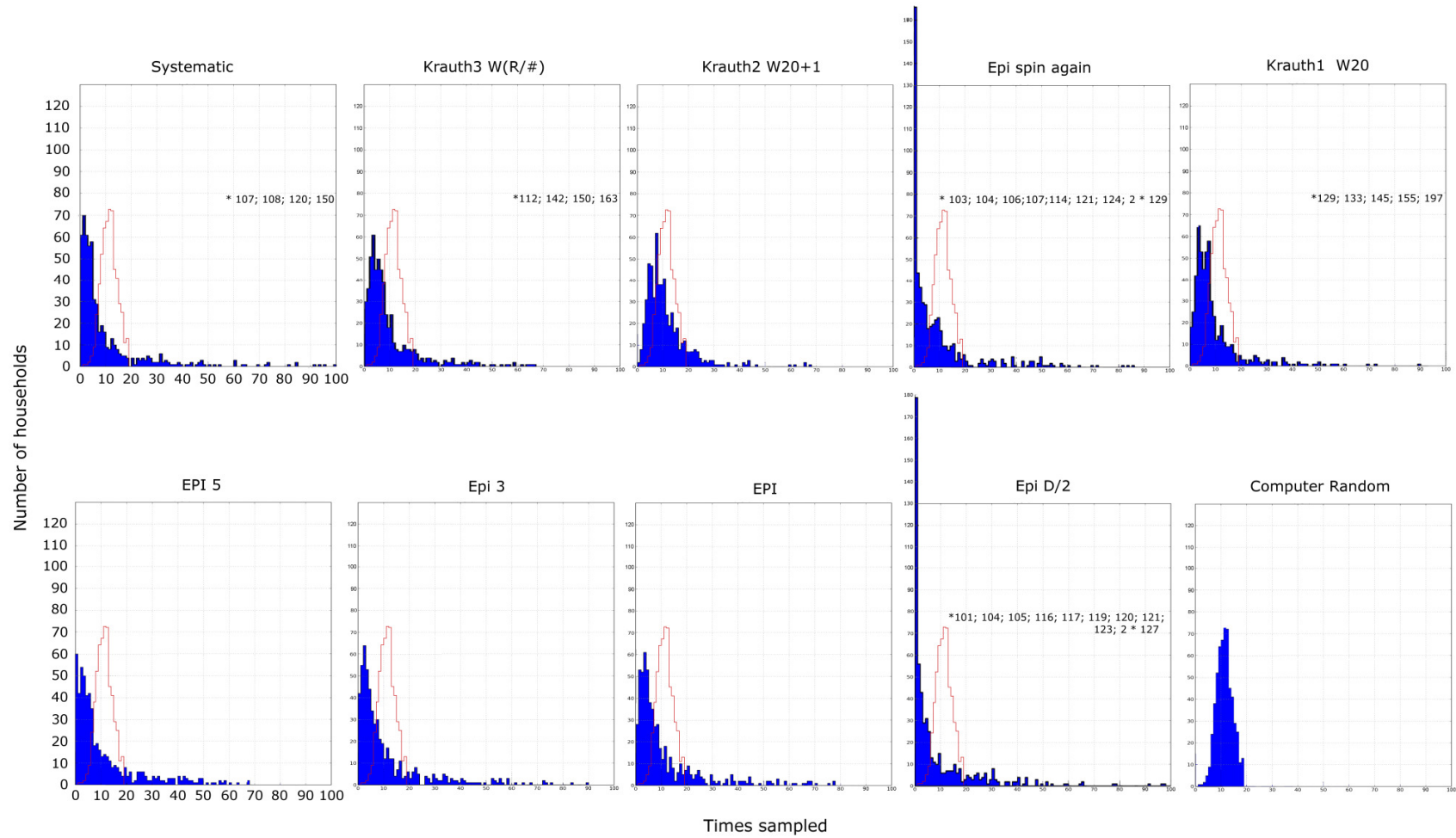


Figure 5.2 Histograms of household inclusion frequency per simulated method at 95% chance of meeting inclusion criteria.

Red, outline from the random sampling; the numbers in the plot area marked with *, relate to houses sampled more often than 80 times and which are out of the range of the plot area.



Figure 5.3 Frequency-distribution of household inclusion over 250 iterations from the random sampling.
Green star, start point; Blue, never included; Black to red, increasing frequency of inclusion

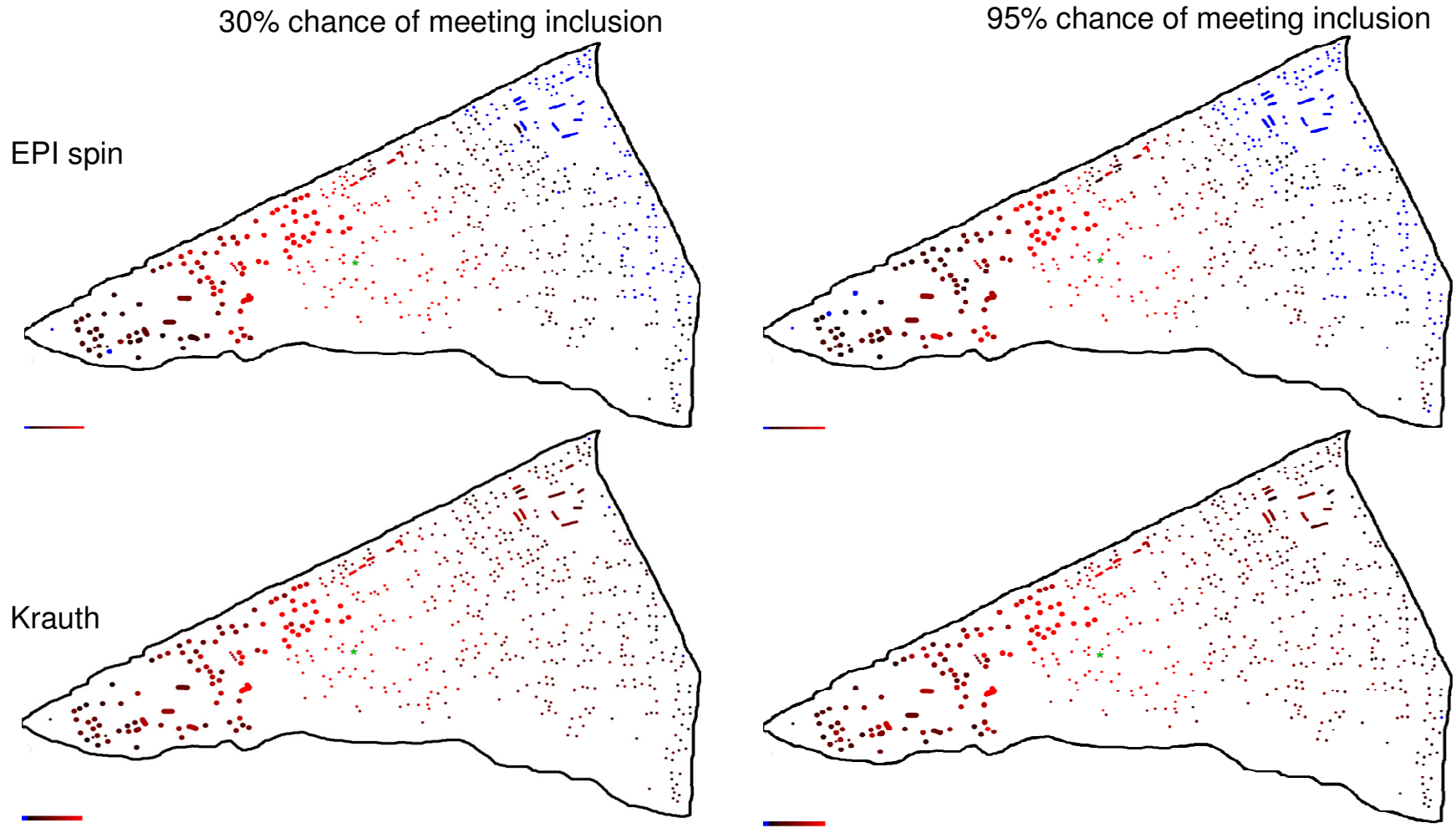


Figure 5.4 Frequency-distribution of household inclusion over 250 iterations.

Top row, **EPI spin again**; Bottom row, Krauth2 (W20+1); Left side, 30% chance of meeting inclusion criteria; Right side, 95% chance of meeting inclusion criteria; Green star, start point; Blue, never included; Black to red, increasing frequency of inclusion

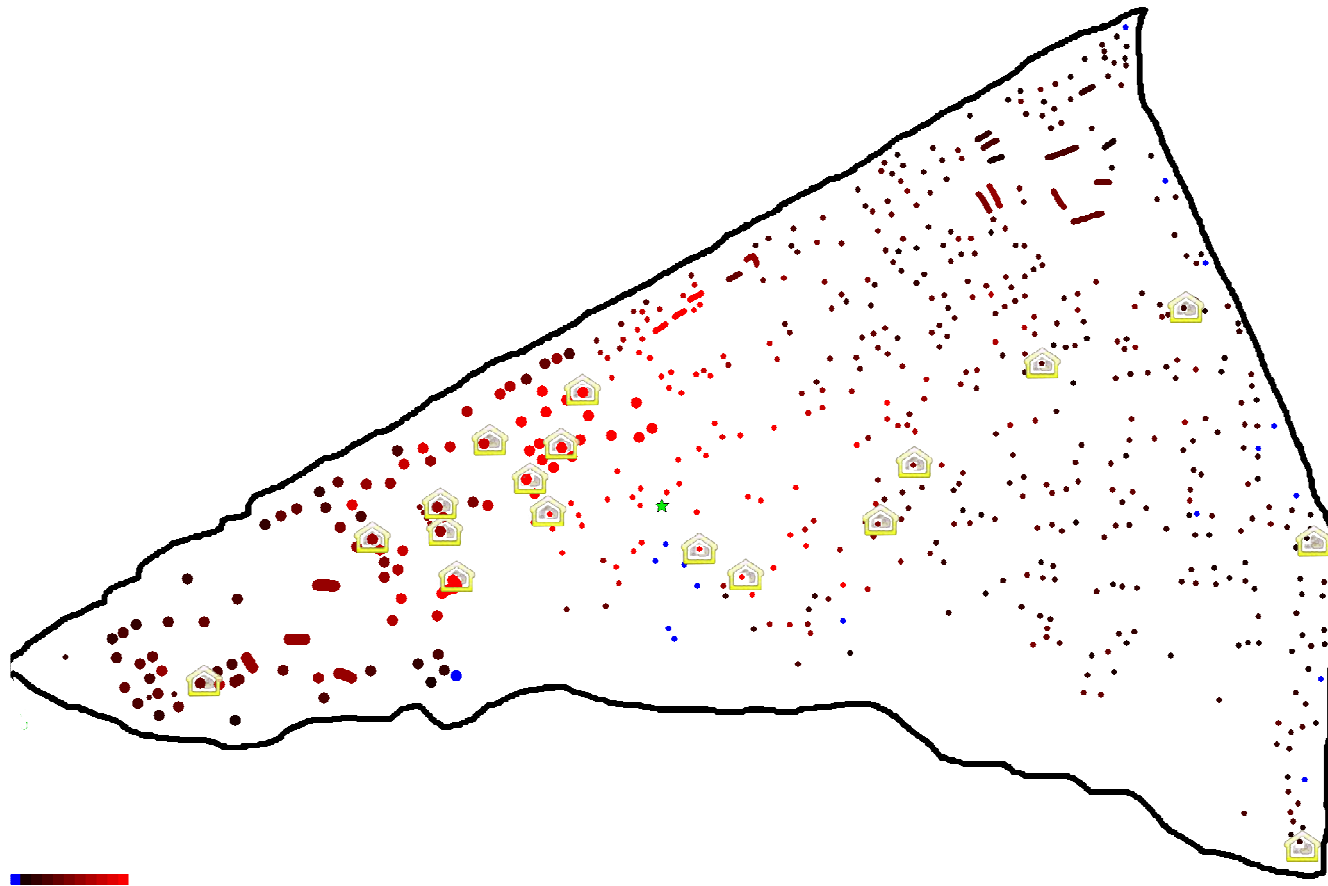


Figure 5.5 Distribution of households actually sampled with the method Krauth1 (W20) over the frequency-distribution map at a 95% chance of meeting inclusion criteria.

Green star, start point; Blue, never included; Black to red, increasing frequency of inclusion; House-symbol, households included with the Krauth1 (W20) method from a true survey in 2013 (courtesy of C. Musard)

5.4.7 Point-pattern analysis

The point-pattern analysis reveals that the village itself shows a certain natural clustering due to its geometry and non-uniform distribution of houses within the village which we named “Intrinsic cluster value”.

The Intrinsic cluster value of the village analysed for this chapter is 1.49 (grid size A/n_1 ; A = area of the village, n_1 = total number of houses within the village). The random sampling within the same village showed an average clustering of 1.182 (range: 0.592 - 2.394, grid size A/n_2 ; A = area of the village; n_2 = 25). All subsequent samplings have to be interpreted in the context of this value. Figure 4.6 and table 4.1 summarize the average clustering for all evaluated sampling methods at a chance of meeting inclusion criteria of 30% and 95%. It can be seen that all methods produced a sample more clustered than the random sample and that this trend increases with increasing chances to meet inclusion criteria. The method **Krauth2 (W20+1)** shows the least average clustering (1.821 (range 0.933 – 3.962) at 30% chance of meeting inclusion criteria and 2.254 (range 0.933 – 6.418) at 95% chance of meeting inclusion criteria) apart from random sampling whereas the method **EPI D/2** shows the highest clustering (2.846 (range 1.342 – 5.599) at 30% chance of meeting inclusion criteria and 4.701 (range 2.652 – 9.283) at 95% chance of meeting inclusion criteria).

Table 5.1 Average clustering values over 250 simulations for all simulated methods at 30% chance of meeting inclusion criteria and 95% chance of meeting inclusion criteria

	inclusion probability 30%		inclusion probability 95%	
	average variance/mean	range	average variance/mean	range
EPI D/2	2.846	1.342 - 5.599	4.701	2.652 - 9.283
EPI	2.733	1.260 - 5.272	4.059	2.325 - 7.891
EPI3	2.733	1.179 - 4.289	3.147	1.588 - 8.710
EPI5	2.733	0.851 - 3.225	2.404	1.342 - 5.581
EPI spin again	2.829	1.588 - 4.944	4.446	2.161 - 8.300
Krauth2 (W20+1)	1.821	0.933 - 3.962	2.254	0.933 - 6.418
Krauth1 (W20)	1.796	0.933 - 4.535	2.912	1.342 - 5.026
Krauth3 (W(R/#))	1.972	0.851 - 4.944	2.979	1.424 - 6.418
Systematic	1.990	1.015 - 3.962	3.154	0.933 - 6.418
Random	1.182	0.592 - 2.394		

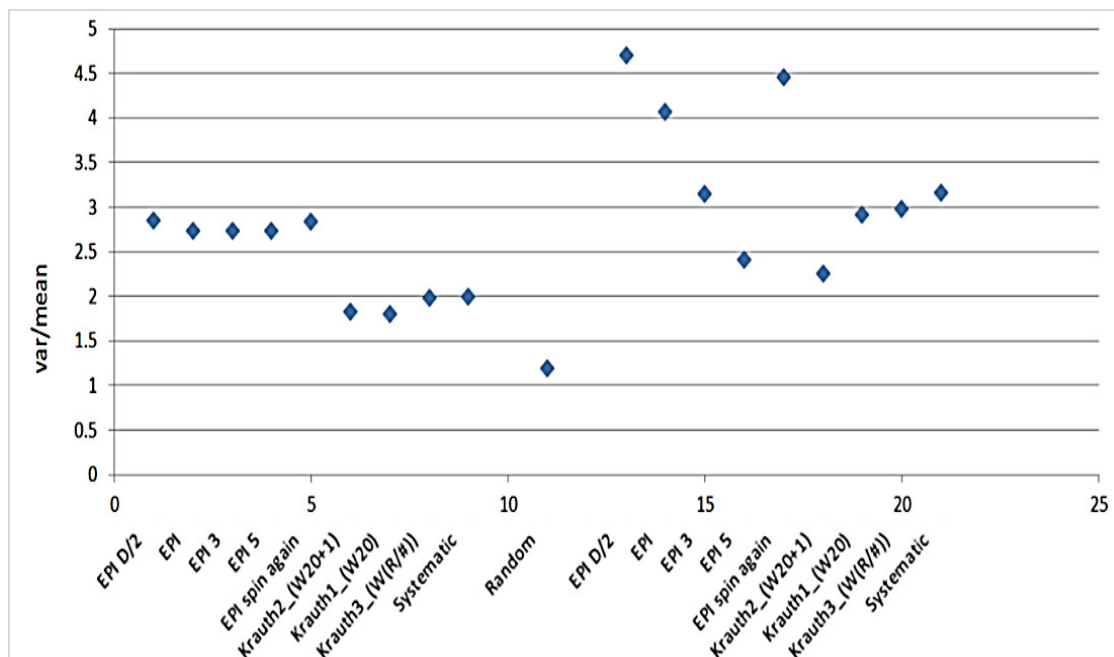


Figure 5.6 Average cluster values over 250 iterations for all simulated sampling methods. left, 30% chance to meet inclusion criteria; Right, 95% chance to meet inclusion criteria

5.4.8 Decision frame

A preliminary decision frame for household sampling methods is being proposed in figure 4.7. Moving down in the levels of the frame indicate a decreasing desirability.

First: wherever possible, a random sampling should be preferred over other methods if a representative sample of the population is needed. Even in a stratified sampling, where different distinctive population groups are to be compared, a random sampling should be drawn within the different strata where possible.

If a list of households exist but is out of date, efforts should be made to update it (i.e. with the help of the local administration or by creating a list with the help of the village inhabitants and/or using a hand-held GPS device and drawing a sketch-map or with the method of Woolse et al. 1956). The same should be done if no list is available.

Second: If a list of households is not available and it is not feasible to create a complete list, divide the cluster into several segments and perform either one of the

compact segment samplings by including whole segments randomly or by sketch-mapping randomly selected segments and then drawing a random sample within each of the selected segments.

Third: If neither of the above is feasible, a spatial sampling method can be employed. Of these, the **Krauth2 (W20+1)** method proved to give results with the fewest systematic exclusions of households and with the least amount of oversampling and clustering compared to other available spatial methods. This method's performance was closest to the results of the random sampling.

If the only goal of a survey is to assess whether there is a certain threshold of an investigated outcome within the village, an LQAS or a double sampling could be a suitable approach.

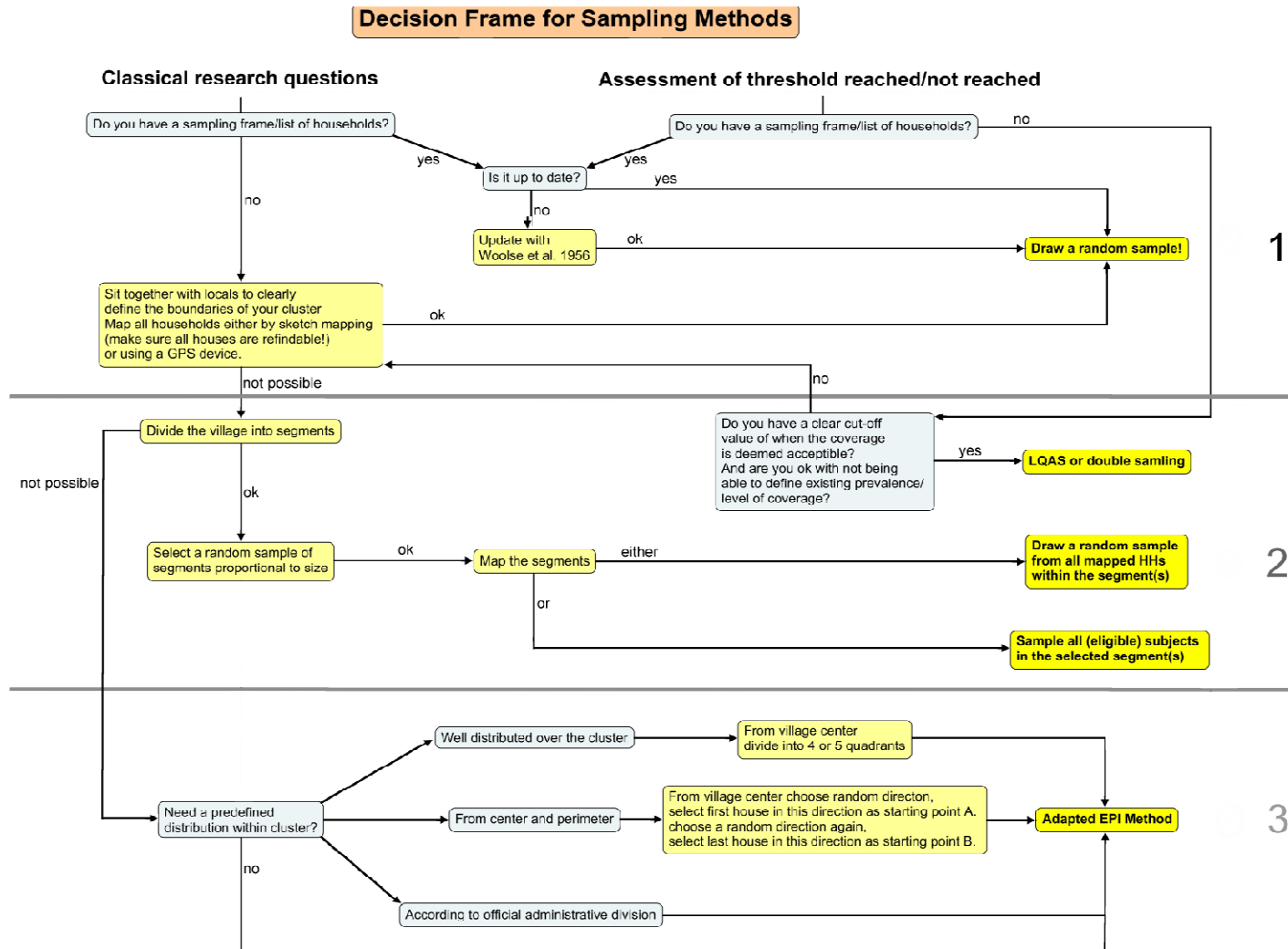


Figure 5.7 Decision frame for choosing household sampling methods in the field

5.5 Discussion

Evaluation of available household sampling methods

Twenty distinct household-sampling methods could be identified in the systematic review apart from a simple random sample. Some of these are forms of cluster samplings (multi stage cluster samples, compact segment sampling, stratified sampling) whereas other methods rely on the acquisition/creation of a sampling frame (relying on national statistics, sketch map villages with or without GPS assistance, or updating an existing, out-of date list), while a third set of methods are spatial methods mostly adapted from the extended Programme of Immunization (**EPI, EPI3, EPI5, EPI D/2, Winkler, Peri, Krauth1** etc.) including some unpublished ones introduced here for the first time. The fourth set of sampling methods pertains to very specific survey questions calling for a stratified sample or allowing for lot quality assessment samples or double sampling.

In order to ensure that every household has the same probability to be included, a simple random sampling should be preferred wherever possible. However, while in theory this does give each house the exact same probability to be sampled, in the reality of the field there are some practical difficulties. First of all it is not always trivial to identify and successfully navigate to a selected household in a given cluster, especially in developing countries with little to no official addresses and in rapidly changing communities and informal settlements including slums (Vanden Eng et al., 2007; Alves et al., 2011). Furthermore, as Woolsey (1956) adequately states, the moment a list is obtained, it is already out of date. Therefore, newer addresses would be systematically excluded from such a random sample. An effort should therefore be made to update a sampling frame and the method of Woolsey (1956). is worthwhile in situations where updating the complete list or obtaining a newer one is not feasible.

A multi stage cluster sampling – including the compact segment sampling - is another method to ensure an equal likelihood of inclusion for most households. By using one of the compact segment sample methods, even households not on the original list of households would have an equal chance of inclusion. (Ikeda et al.,

2011) even argue that a multi stage cluster sampling can give better results as a systematic random sample of the smallest sampling unit. Two factors have to be considered for segment sampling approaches. When the division into segments is based on administrative units such as city quarters, the borders of these segments are not always easily identifiable. Also informal or illegal settlements would be excluded from such a sample as would households situated slightly outside of the administrative segments and the researcher would have to define how to treat these households. Additionally, since segments are likely of different size, some information about the number of households within each segment is necessary and the sampling should be proportional to size. When the division into segments is being done by the research team, easily identifiable borders can be used, and segments of approximately equal size can be created. However there is a risk that households at the far edge of the village or slightly outside the main area of the village would be lost and there needs to be decision in how to deal with them. Moreover, the accuracy of division will be largely dependent on the investigator who is performing the work. For all segment sampling methods, either all households from the selected segments would be included or the selected segments would be mapped and a random sample of households within the segments would be drawn. By sketch mapping only selected segments, the mapping effort can be reduced compared to mapping the whole village.

The usefulness for stratified sampling and the scope of application has been discussed elsewhere and belongs to textbook knowledge (Fowler, 2013; Levy and Lemeshow, 2013). Nevertheless the practical implementation of a stratified sampling is largely dependent on the availability of a list of households. Moreover, some information about the individuals living inside these households is needed as well. Stratified sampling thus faces some of the same problems as the simple random sampling. However, for more common strata within the population (such as gender or age) a stratified sample can be achieved by either one of the spatial methods whereby sampling is continued until the desired sample size in each stratum has been reached. Although it needs some additional effort, even a sequential random sampling would be feasible where, in a first round, a random sample is drawn and all

households are being investigated for individuals who meet the inclusion criteria. In case the number of included individuals is not sufficient, a second random sample would be drawn from the same list, excluding already investigated household. These steps are then repeated until the desired sample size has been reached. However, it would exclude households which are vacant at the time the investigator comes by and no effort would be done to include this household. This in turn could exclude certain population groups (students, worker etc.) from the sample.

Mapping the entire village (or segments thereof) using a hand-held GPS device or Tablet computer has been proposed by Vanden et al. (2007). This facilitates the identification and navigation to a once sampled household. The Tablet computer can also assist in the actual random sampling as long as the researcher ensures to use a suitable programme or app for this endeavour (L'Ecuyer, 2001; McCullough and Heiser, 2008). The usefulness of such a GPS device, however, depends on the density of the village or segment. Especially in a highly packed village or in a slum, the imprecision of the GPS position is far greater than the actual distance between the houses. Yet, with dedicated investigators and adequate precision of the measurement, the GPS might prove to be a viable tool within a less densely populated village. Otherwise, a hand drawn sketch map, as proposed by Alves et al. (2011) might be preferable if correctly executed.

The LQAS and double sampling method are suitable methods for a rapid assessment of whether a certain threshold of an investigated outcome has been reached by the village. This could serve either for a rapid assessment of the need for an intervention or to assess whether an implemented intervention has reached a certain proportion of the village. However, these methods do not allow for the quantification of the outcome. Also the sampling is subjected to the same problems as the spatial sampling approaches, where households closer to the start point of the sampling are being over represented. This could lead to substantial bias if households at the outer rim of the village are less exposed to an intervention as the centre. With some efforts and by combining the LQAS method with the compact segment sampling, these problems could be alleviated.

For spatial methods, we have found seven distinct adaptations to the original sampling method proposed by the extended programme of immunization and added some additional ones proposed here for the first time. The EPI method has well known disadvantages (Anker, 1991; Bennett et al., 1994; Bostoen and Chalabi, 2006). For one, it is only suitable for very tight inclusion criteria as otherwise the very centre of each village would be extremely overrepresented. The **EPI3** and **EPI5** methods have been suggested to overcome this issue and they indeed manage to reduce the number of systematically excluded households as well as the extreme oversampling of the village centre in our simulations. Second, the amount of clustering is huge, especially if the method is performed by only one investigator. This can be slightly amended by using several investigators (or one person performing the same method several times in different directions). Interestingly and to our great surprise, one of the methods proposed to circumvent some of these problems, namely the **EPI spin again**, had detrimental effects on all sampling evaluation parameters. Extreme numbers of households were systematically excluded from the **EPI spin again** sample, especially with increasing likelihoods to meet the inclusion criteria. This is due to the fact that the households around the starting point are severely over-represented in the sample. Some households have been included in up to 129 out of 250 iterations (at 95% chance of meeting the inclusion criteria). Also the amount of clustering is highest with this method, indicating that each sample drawn with this method will always be concentrated around the starting points. Equally surprising is the bad performance of the **EPI D/2** method, where the start point of the **EPI** sampling of is determined by a random number between 1 and $D/2$. The method by Winkler et al. (2010) is very similar and we expect that it would yield comparable results, although this method has not yet completed simulation. However, two factors have to be considered in the interpretation of the simulations of the **EPI D/2** method. First of all, the direction in which the houses are counted is selected randomly. The size of the dice with which the start point defined is therefore largely depending on the geometry of the village and the chosen direction. The Start point used in the simulation is the actual point that has been indicated to us as a central place in the village by the village leaders

(Krauth & Musard 2015). One border of the village is rather close to this start point and there are only a few houses between the border and the start point for many possible directions. The resulting dice to select the start point risks to be unduly small. A real investigator in the field might or might not be able to identify this problem and circumvent it by forcing a longer diameter. Secondly, for counting houses along the diameter within the simulation, it has been defined that an investigator would count every house within 7 meters on either side of the trajectory. Were this parameter to be increased, the results might look differently.

The Method that seemed to work best is the method we titled **Krauth2 (W20+1)**, where a random dice with 20+1 sides (in reality a pouch full of lots) was rolled after each selected household. Sides 1-20 decided which house would be sampled next whereas the 21st side indicated that a new direction had to be randomly chosen by spinning a pen again. While there is still considerable oversampling happening especially around the starting point, the **Krauth2 (W20+1)** method shows slightly less oversampling compared to most other method apart from a simple random sampling. More importantly, the number of houses systematically excluded is substantially lower, with only 2 exclusions after 250 sampling iterations (at a 95% chance to meet inclusion criteria). Although, due to the over-representation of the area around the starting point, households do not have equal likelihoods to be sampled, almost all houses have at least some chance to be in the sample. This is a feature that is otherwise only achieved by simple random sampling which does in fact give equal chances to all households but with the practical problems discussed above. Clustering of the included households is also less with the **Krauth2 (W20+1)** method compared to others. The method can be further adapted to research questions aiming to include primarily persons from a specific location in the village, for example by defining borders of segments i.e. areas near big roads or at the outskirts of the village (Winkler et al., 2010), and having each investigator perform the method within the catchment area of the segment.

Limitations

Most importantly for any of the mentioned household-sampling methods discussed here, any researcher needs to have a clear definition of household suitable to his research question and a good strategy for the inclusion of individuals from the household. For the purpose of this work, we have made the simplified assumption that one house equals one households. One widely used definition of a household as a group of people whose meals are being prepared by the same person(s) is a very practical one for the work in developing countries (Bennett et al., 1991). It nevertheless comes with some well-known disadvantages deriving from the nature of life in developing countries where households are rarely operating isolated. Yet, these issues go beyond the scope of this manuscript and are discussed elsewhere (Ünalán, 2005; Leone et al., 2010).

For the purpose of our simulation, we have defined every building in a village as a household and there are assumed to be no unoccupied houses in the village. While this is clearly not the case in real-live villages, it is unlikely to influence the sampling if performed correctly. The investigator would simply identify the building as one not made for living or would find out upon investigation and would then simply not count such a building during sampling.

One bigger concern in the simulations is the visibility of houses. For simulation, we determined that any house within 7 meters on either side from the trajectory of the investigator will be counted during the sampling. In reality, a house hidden behind another house would unlikely be counted due to lack of visibility. On the other hand, a house standing a little farther away but with nothing in between to block the investigator's view, would not be identified by simulation but would likely be counted by the real investigator. Thus some hidden households in a village would risk systematic exclusion with every spatial sampling method (but not with random sampling) whereas other houses, excluded from the simulated sample, would be included in reality.

The second issue concerns the presence of streets. For the purpose of this simulation, we have assumed that the investigators would follow the chosen direction in a straight line from the start point to the edge of the village. In reality,

however, the investigators would follow streets and little paths in the rough direction chosen. The exact decision which paths to follow would no longer be random but based on the investigators preferences which could lead to a biased sample. In any of the spatial methods, this will be an issue. Even assuming investigators would be dedicated to go in a straight line, there will be blockages and obstacles in their way. Furthermore, accurately keeping a direction once chosen is highly error prone even if the investigators were to be equipped with a compass for guidance. This is to say that random sampling would still be preferable, provided the practical difficulties are being addressed properly, even if a spatial method would manage to perform to the standards of a random sampling.

One last important consideration needs to be kept in mind. Any sampling, whether random or spatial, will be highly influenced by the correct execution and the dedication on the part of the investigators executing the sampling. Great efforts and considerable time investments need to be made to adequately train investigators. Investigators need to fully understand not only the procedures and protocols but also the underlying principles and reasons for why the sampling method is the way it is and why this is important. Irrespective of whether the investigators are students in the field or simply paid worker with no formal training in Epidemiology, with adequate training we can reduce the probability that they make assumptions about the method and change details autonomously because they think, mistakenly, that it would lead to the same result. We have made the experience that the spatial methods used by our research team (Winkler et al., 2010; Krauth et al., 2015b) are easy to be implemented in the field. Each investigator can simply be equipped with a pen and a pouch of numbered lots alongside the rest of their survey materials.

As an outlook for future work on the subject, the methods performing best in the general simulation could be simulated in a village with known population features, for example in a village within a health and demographic surveillance system such as the Taabo HDSS in Côte d'Ivoire (Koné et al., 2015). This would allow us to compare statistical outcomes between different samples derived with the various sampling methods as was, in parts, done by Bennett et al. (1994).

Note: *The simulation results and subsequent point-pattern analysis presented and discussed in this chapter are preliminary results. Not all sampling methods identified during the literature review have completed simulation. All methods will be fully simulated and analysed in the future. Additionally, due to resource constraints in terms of computational power, only 250 iterations have been simulated for each method so far. This will be stocked up to a full 1'000 iterations for the full set of methods to obtain more adequate results. The final results will then be reported and published in a peer-reviewed scientific publication.*

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6. All that is blood is not schistosomiasis: considerations for the use of reagent strip testing for urogenital schistosomiasis with special consideration to very low prevalence settings

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6.1 Abstract

Background: Reagent strip testing for microhaematuria has long been used for community diagnosis of *Schistosoma haematobium*. Sensitivities and specificities are reasonable, and hence, microhaematuria can serve as a proxy for *S. haematobium* infection. However, assessment of test performance in the context of the underlying *S. haematobium* prevalence is rare and test parameters other than sensitivity and specificity have been neglected.

Methods: Data about the association between microhaematuria and urine filtration results from three studies were compared and put into context with findings from a recent Cochrane review. Data were stratified by *S. haematobium* prevalence to identify prevalence-related differences in test performance. Kappa agreement and regression models were employed to compare data for different *S. haematobium* prevalence categories.

Results: We found a “background” prevalence of microhaematuria (13%, on average) which does not seem to be associated with schistosomiasis in most settings, irrespective of the prevalence of *S. haematobium*. This background level of microhaematuria might be due to cases missed with urine filtration, or alternative causes of microhaematuria apart from *S. haematobium*. Especially in very-low-prevalence settings, positive results for microhaematuria likely give an inaccurate picture of the extent of *S. haematobium*, whereas negative results are a sound indicator for the absence of infection.

Conclusions: Reagent strip testing for microhaematuria remains a good proxy for urogenital schistosomiasis, but implications of test results and scope of application differ depending on the setting in which reagent strips are employed. In very low prevalence settings, microhaematuria is an unstable proxy for urogenital schistosomiasis and treatment decision should not be based on reagent strip results alone. Our findings underscore the need for highly accurate diagnostic tools for settings targeted for elimination of *Schistosoma haematobium*.

Keywords: Chad, Côte d’Ivoire, Diagnosis, Microhaematuria, Reagent strip testing, *Schistosoma haematobium*, schistosomiasis

6.2 Introduction

Since the early 1980s, reagent strip testing for microhaematuria has been used as an indirect diagnostic assay for *Schistosoma haematobium* (Mott et al., 1983; Mott et al., 1985a). Indeed, various studies validated reagent strips against standard urine filtration and concluded that the detection of microhaematuria is a valid proxy for urogenital schistosomiasis and related morbidity (Stephenson et al., 1984; Lengeler et al., 1993; King and Bertsch, 2013; Ochodo et al., 2015). In a recent Cochrane review it has been summarised that reagent strip testing for *S. haematobium* diagnosis has an overall sensitivity and specificity of 75% and 87%, respectively (Ochodo et al., 2015). For specific settings it was suggested that reagent strip testing can be used for individual diagnosis and treatment decision (Mott et al., 1985b; Taylor et al., 1990), while other groups described reagent strip testing more conservatively as a useful tool for estimating community prevalence (Lengeler et al., 1993; Mtasiwa et al., 1996; Robinson et al., 2009).

Interestingly, in most settings, there was some proportion of ‘false positive’ (FP) reagent strip results where microhaematuria could not be associated with *S. haematobium* through reference microscopy (King and Bertsch, 2013; Ochodo et al., 2015). Even after the administration of praziquantel, the prevalence of microhaematuria rarely goes to zero and authors have suggested several explanations for this observation. One suggestion is that some *S. haematobium* infections were missed by microscopy. Especially in low-prevalence settings, *S. haematobium* egg output is generally low and thus hard to be detected by a single filtration of only 10 ml of urine (Mott et al., 1985a; Kosinski et al., 2011). Repeated urine sampling and use of more sensitive diagnostic assays might remedy this issue (Taylor et al., 1990; Kosinski et al., 2011; King and Bertsch, 2013). Another explanation is that bladder lesions and associated microhaematuria persisted longer than the actual excretion of eggs into the bladder (Doehring et al., 1985). A third reason why some microhaematuria is unrelated to urogenital schistosomiasis is that residual menstrual blood or pregnancy in females results in positive reagent strip results (Brown et al., 2005). Fourth, it has been noted that tests from different

manufacturers performed differently in their ability to detect microhaematuria. For example, the Hemastix® (Bayer Diagnostics; Basingstoke, United Kingdom) proved less sensitive than the Combur 9 Test® (Roche Diagnostics; Basel, Switzerland) for microhaematuria and *S. haematobium* infection as confirmed by microscopy (Lengeler et al., 1993). Finally, *S. haematobium* infection is not the only aetiology of microhaematuria (Hatz et al., 1990; McDonald et al., 2006).

The purpose of this study was to assess the diagnostic accuracy of reagent strips for microhaematuria with particular consideration of settings characterised by low levels of *S. haematobium* prevalence. We addressed three specific research questions. First, does the level of microhaematuria correspondent to the level of *S. haematobium* infection in low-prevalence settings? Second, is microhaematuria that seems unrelated to *S. haematobium* merely due to missed cases? Third, can microhaematuria be used as a proxy for *S. haematobium* in low-prevalence (<20%) areas or settings with very low-prevalence that are targeted for elimination (<5%)?

6.3 Materials and methods

6.3.1 Ethics statement

The three study protocols from which original data were obtained for the current analysis (twice Côte d'Ivoire, once Chad) were approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland) and received clearance from the ethics committees of Basel (EKBB; reference nos. 377/09 and 64/13) and the national ethics committee in Côte d'Ivoire (reference no. 32-MSLS/CNERdkn and 1993 MSHP/CNER). In Chad, research authorization including ethical approval was granted by the Direction Générale des Activités Sanitaires in N'Djamena (reference no. 343/MSP/SE/SG/DGAS/2013).

District, regional and local authorities, village chiefs, study participants and parents/guardians of individuals aged below 18 years were informed about the purpose, procedures and potential risks and benefits of the study. Information was provided in the national language (French), as well as common languages spoken in southern and northern Côte d'Ivoire (Baoulé, Dioula/Peulh/Fula and Senoufo) and

the Lake Chad area (Arab, Dioula/Peulh/Fula and Kanembou). All authorities and camp/village chiefs were asked for their written or oral consent for the conduct of the study in the respective administrative area. In Côte d'Ivoire, written informed consent was obtained from all participants and the parents/guardians of minors. In case of illiteracy, consent was given in front of an impartial witness of the participant's choosing who signed in the name of the participant. In Chad, informed consent was signed by the camp leader in the presence of an impartial witness after discussion within the group. Due to high illiteracy rates, participating individuals consented orally. These consent procedures had been approved by the respective ethics committees.

Participation was voluntary and there were no further obligations for those who withdrew from the study. All results were coded and treated confidentially. At the end of the studies, all positive individuals were offered a single 40 mg/kg oral dose of praziquantel free of charge.

6.3.2 Data

Côte d'Ivoire

During the course of a relatively large study performed in 2014/2015 in the Tchologo region in northern Côte d'Ivoire (Krauth et al., 2015a), participants from 28 randomly selected villages, including one to two unofficial settlements in close proximity to the villages, were asked to provide a urine sample. Sample collection was performed throughout the day with 47% of all samples collected between 10 a.m. and 2 p.m., 83% before 4 p.m. and 98% before 6 p.m. Urine samples were transferred to nearby laboratories in Korhogo and Ouangolodougou, where they were subjected to reagent strip testing (Hemastix®, Bayer Diagnostics; Basingstoke, United Kingdom) and the standard urine filtration method. In brief, reagent strips were performed according to the manufacturer's instructions and results recorded as negative, trace, 1+, 2+ and 3+. With regard to the urine filtration method, one urine sample was examined with a single filtration. In brief, 10 ml of a vigorously shaken specimen were pressed through a 13 mm diameter Nylrel filter with a mesh size of 20 µm (Sefar AG; Heiden, Switzerland), placed on a microscope slide, stained with a drop of Lugol iodine and

then examined under a microscope systematically enumerating *S. haematobium* eggs. All parasitological examinations were performed by the same technician and laboratory assistant. 15% of the slides were subjected to quality control. In case of discrepancies between the two readings, all slides of the respective day were read a second time.

Additionally, we re-examined data from a study conducted in 2010 in Grand Moutcho in south Côte d'Ivoire that assessed the dynamics of *S. haematobium* egg output following oral administration of a single dose of praziquantel (40 mg/kg). Details of this study have been published elsewhere (Stete et al., 2012). In brief, urine samples of two consecutive days were collected from 124 children aged 7-15 years during a baseline survey. Each sample was tested using urine filtration with Lugol iodine staining and reagent strip tests (Combur-7-Test®, Roche Diagnostics; Basel, Switzerland) for microhaematuria, proteinuria and leukocyturia. All *S. haematobium*-positive children (n = 90) were treated. Subsequently, single urine samples were collected from all treated children every day for the first 2 weeks and then twice a week up to 8 weeks post-treatment. All samples were subjected to urine filtration and reagent strip testing for microhaematuria, proteinuria and leukocyturia (Combur 7 Test®).

Chad

Urine filtration of 10 ml or whole urine samples from single urine samples (without Lugol iodine staining) and reagent strip testing (Hemastix®, Bayer Diagnostics; Basingstoke, United Kingdom) was likewise performed in the Lake Chad area, where 19 randomly selected groups of mobile pastoralists from four ethnic groups were enrolled in 2013 and 2014. Participants from Chad were followed up twice, 6 and 12 months after the baseline survey. Participants found positive for schistosomiasis with urine filtration and/or with a point-of-care cathodic circulating antigen (POC-CCA) urine cassette test for the detection of *Schistosoma mansoni* infection, were treated with a single dose of praziquantel (40 mg/kg). All parasitological tests in Chad were performed on the spot in a small, mobile

laboratory by one of the authors (HG) with assistance from experienced laboratory technicians.

Published data from recent Cochrane review

Relevant data from a recent Cochrane review entitled “Circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas” (Ochodo et al., 2015) were extracted and re-organised by prevalence to put our data in the context of other published literature.

6.3.3 Statistical analysis

Data were analysed using Stata/IC version 12.1 (StataCorp; College Station, TX, United States of America). A random effects logit regression was employed on our original data with village/camp included as random effect to calculate the relationship between microhaematuria and *S. haematobium* prevalence, the latter confirmed by urine filtration. Reagent strips were read qualitatively (positive or negative). Trace-positive reagent strips were considered as positive. Of note, distinguishing between reagent strip read-out intensities did not change the results notably, except reducing the sample size.

Data from the recent Cochrane review were entered as the number of ‘true positives’ (TP), ‘false positives’ (FP), ‘false negatives’ (FN) and ‘true negatives’ (TN), as reported in the Cochrane review. Subsequent percentages were calculated from these numbers and compared to our data. To examine test performance for different prevalence levels, all baseline and follow-up survey results were grouped according to prevalence categories (0-5%, 5-10%, 10-20%, 20-50% and 50-100%).

6.4 Results

6.4.1 Study participants and prevalence

In the Tchologo region of northern Côte d'Ivoire, 8-33 individuals per village (including nearby Peulh camps) were included in the study. Overall, there were 831 participants and among them, 809 provided a urine sample. Single reagent strip reading and urine filtration were available from 805 and 802 of the participants, respectively, and 801 participants (493 females and 308 males) had complete data. The prevalence of *S. haematobium* based on single urine filtration was 2.2%, whereas a positive reagent strip result was noted in 19.5% of the participants.

In Grand Moutcho, south Côte d'Ivoire, 124 school-aged children (62 females and 62 males) participated in a baseline survey. The prevalence of *S. haematobium* and microhaematuria was 74% and 62%, respectively at day 1 of the baseline survey and 70% and 66%, respectively at day 2 of the baseline. The overall prevalence of *S. haematobium* and microhaematuria for both baseline days combined was 79% and 71% respectively (Stete et al., 2012).

In Chad, a total of 402 participants provided a urine sample and 369 of them (181 females and 188 males) were tested with reagent strips and urine filtration. 214 individuals (62.9%) provided a subsequent sample for the first follow-up and 75 (22.1%) provided a sample for the second follow-up. A total of 60 individuals were treated with praziquantel at baseline as they had a positive test result (either urine filtration or POC-CCA for *S. mansoni*) or because health personnel suggested treatment based on clinical assessment. Urine filtration revealed prevalence of *S. haematobium* of 7.9% at baseline, 2.7% after the first and 2.6% after the second follow-up. Microhaematuria was found in 21.1% at baseline and in 12.7% and 10.4% after the first and second follow-up, respectively (Figure 5.1). In all settings, individuals with light intensity infections (egg excretion <50 egg per 10 ml of urine) had a negative reagent strip result significantly more often ($p < 0.005$) than individuals with heavy infection intensity (egg excretion ≥ 50 egg per 10 ml of urine).

Of note, the prevalence of *S. mansoni*, as assessed with double Kato-Katz thick smears from a single stool sample in northern Côte d'Ivoire was 0.8%. In Chad,

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single Kato-Katz thick smears and an ether-concentration method revealed a prevalence of *S. mansoni* of 0.3% (Figure 5.1).

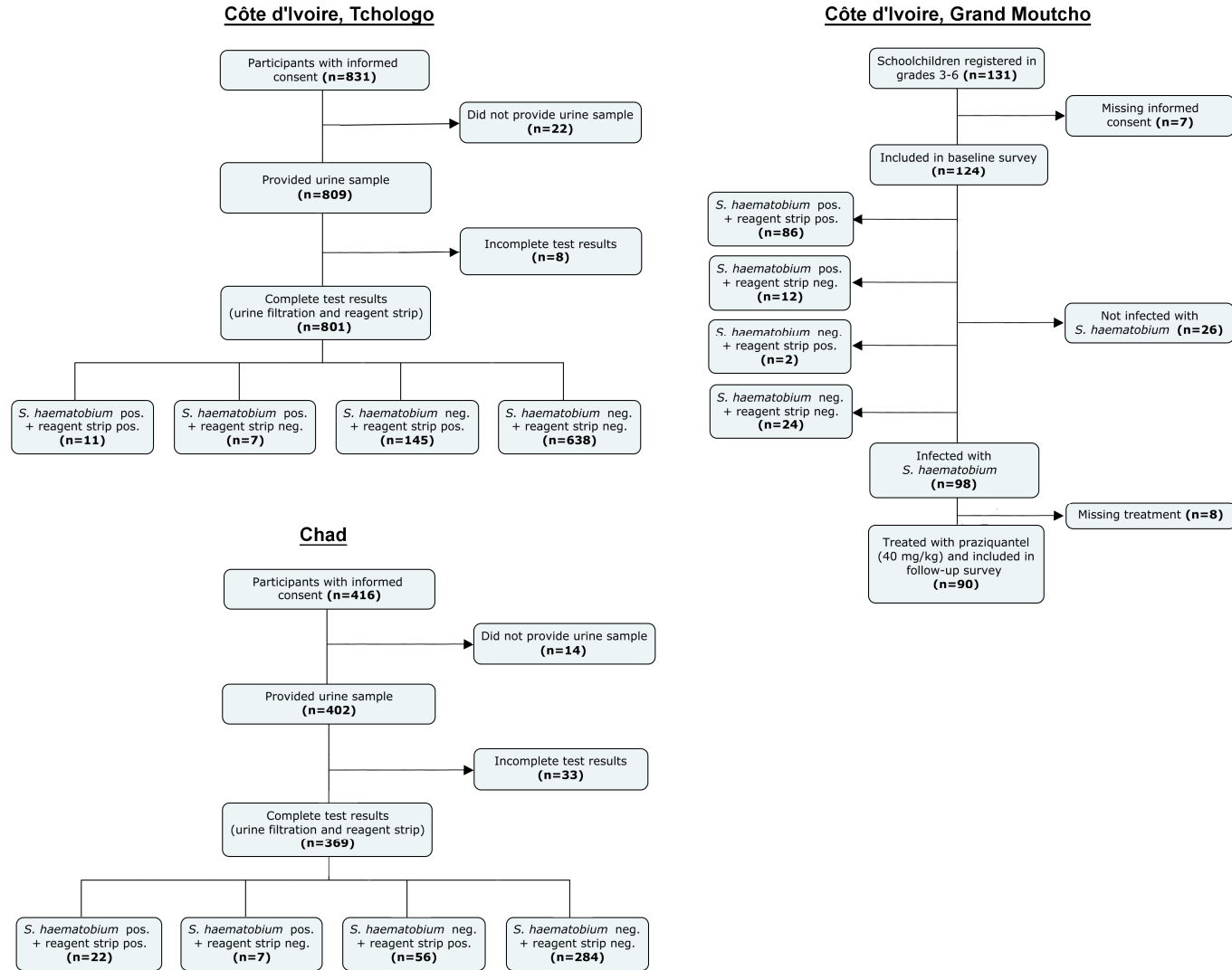


Figure 6.1 Flow chart showing the study cohort and compliance with emphasis on the three different samples considered in the analysis

6.4.2 Performance of reagent strip testing compared to urine filtration

In our studies, reagent strip testing resulted in reasonable sensitivities of 61.1% (north Côte d'Ivoire), 75.9% (Chad) and 87.8% (south Côte d'Ivoire). Specificities were somewhat higher; 81.5% (north Côte d'Ivoire), 83.5% (Lake Chad) and 92.3% (south Côte d'Ivoire).

A random effects logit regression between reagent strip and urine filtration outcome with village included as random effect, revealed an odds of having a positive filtration when reagent strip was positive of 7.4 (95% confidence interval (CI): 2.3-23.8) in northern Côte d'Ivoire, 86.0 (95% CI: 18.0-410.8) in southern Côte d'Ivoire and 20.7 (95% CI: 7.5-57.3) in Chad. The respective Kappa agreements between the filtration results and the reagent strip results all showed nearly perfect agreement; 0.81 (northern Côte d'Ivoire), 0.88 (southern Côte d'Ivoire) and 0.83 (Chad) (Landis and Koch, 1977).

The positive predictive value (PPV), which indicates the likelihood (in %) of being infected with *S. haematobium* if tested positive for microhaematuria, differed greatly from one study to another (7.1% in north Côte d'Ivoire, 28.2% in Lake Chad area and 97.7% in south Côte d'Ivoire). The negative predictive value (NPV; likelihood of not being infected with *S. haematobium* if tested negative with reagent strip), on the other hand, was very high in all of our surveys. A detailed description of test performance in each of the three study sites including the follow-up surveys at Lake Chad are summarised in Table 5.1. The model predicted odds for having microhaematuria despite a negative urine filtration result at baseline were 7.1 in northern Côte d'Ivoire, 28.2 at Lake Chad and 79.0 in southern Côte d'Ivoire.

Table 6.1 Reagent strip test performance in the three study sites.

Study	TP	FP	FN	TN	Egg positive	Microhaematuria	Sensitivity	Specificity	PPV	NPV
Côte d'Ivoire, Tchologo	11	145	7	638	2.2%	19.5%	61.1%	81.5%	7.1%	98.9%
Chad baseline	22	56	7	284	7.9%	21.1%	75.9%	83.5%	28.2%	97.6%
Chad 1st follow-up	4	24	2	190	2.7%	12.7%	66.7%	88.8%	14.3%	99.0%
Chad 2nd follow-up	1	7	1	68	2.6%	10.4%	50.0%	90.7%	12.5%	98.6%
Côte d'Ivoire, Grand Moutcho	86	2	12	24	79.0%	71.0%	87.8%	92.3%	97.7%	66.7%

PPV, positive predictive value; NPV, negative predictive value; TP, true positive (positive with reagent strip and filtration), FP, false positive (positive with reagent strip, negative with filtration); FN, false negative (negative with reagent strip, positive with filtration); TN, true negative (negative with both, reagent strip and filtration)

6.4.3 Test performance by prevalence

Data obtained in our studies and data from the Cochrane review showed that, regardless of the setting, around 15-20% of the subjects had microhaematuria whenever the prevalence of *S. haematobium* was below 21%. Above this prevalence level, microhaematuria increased in parallel to *S. haematobium* (Figure 5.2).

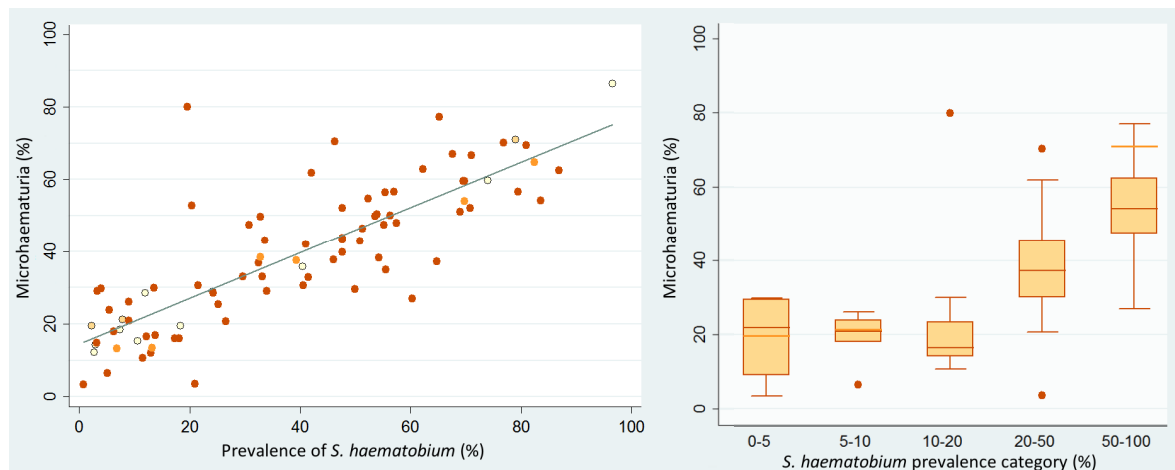


Figure 6.2 Average microhaematuria over *S. haematobium* prevalence from all surveys as scatter plot and box plot.

■ Cochrane data without treatment; ● Cochrane data post-treatment; □ own data without treatment; ○ own data post-treatment.

Light-orange lines in the box plot refer to data from our three surveys.

While sensitivity and specificity were relatively stable over various prevalence levels, PPV and NPV are inherently dependent on prevalence (Figures 5.3 and 5.4). However, the percentage of microhaematuria seemingly unrelated to *S. haematobium* was stable over different prevalence ranges when taken into account that it will be hidden for higher prevalences.

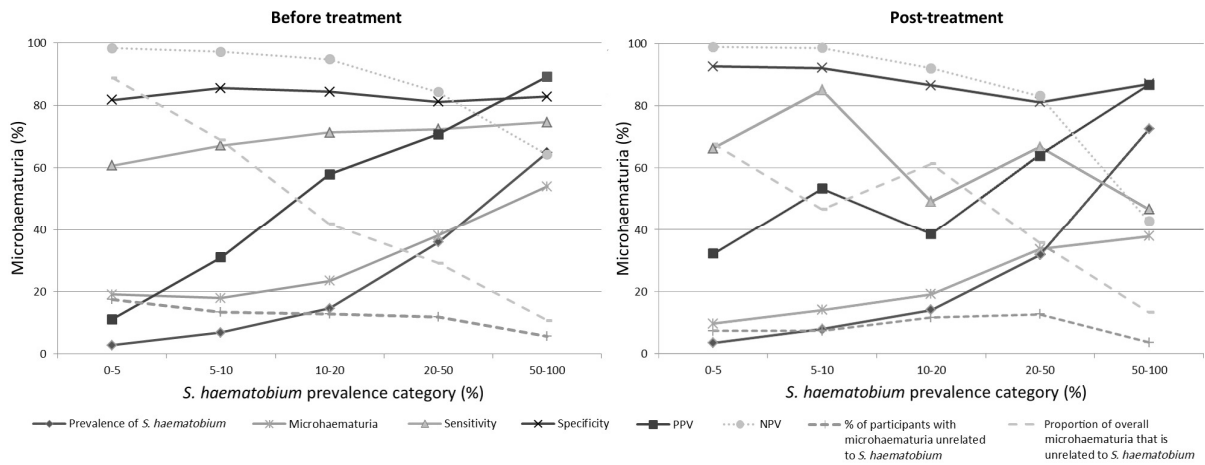


Figure 6.3 Test parameters (arithmetic mean of all studies) at different prevalence categories before and after treatment.
 Each of follow-up survey in our studies was counted as separate survey

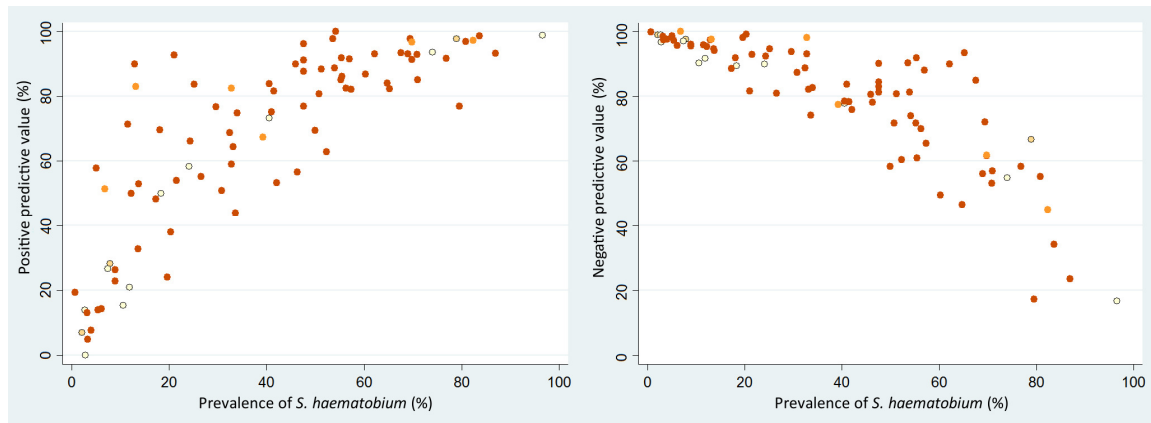


Figure 6.4 Positive and negative predictive value over *S. haematobium* prevalence
 ■ Cochrane data without treatment; ■ Cochrane data post-treatment; ◆ own data without treatment;
 ○ own data post-treatment.

Treatment prior to testing did not substantially alter the picture and seemingly unrelated microhaematuria, although slightly less, showed the same pattern across prevalence ranges (Figure 5.5). When the dynamics of microhaematuria was examined over an 8-week period post-treatment for children who tested positive for *S. haematobium* at baseline and were given a single 40 mg/kg oral dose of praziquantel, it was found that, while the prevalence of microhaematuria drops about similarly as the egg output over time, the level of microhaematuria seemingly unrelated to *S. haematobium* egg output quickly reached the same overall background level as found in other studies. The model-predicted odds for having microhaematuria despite a negative filtration result, reached a stable level after the first week post-treatment (Figure 5.6).

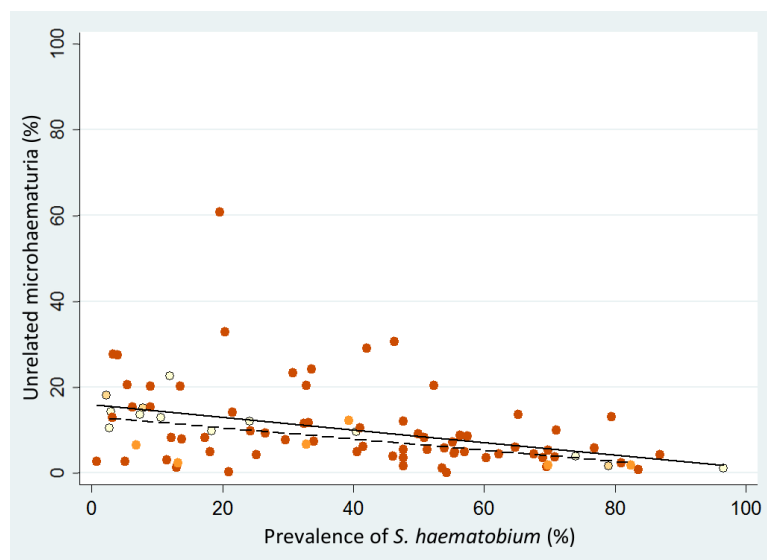


Figure 6.5 Microhaematuria not associated with *S. haematobium*, stratified by *S. haematobium* prevalence in the study

■ Cochrane data without treatment; ● Cochrane data post-treatment; ■ own data without treatment; ● own data post-treatment.

Solid regression line, all studies; dashed regression line studies post-treatment.

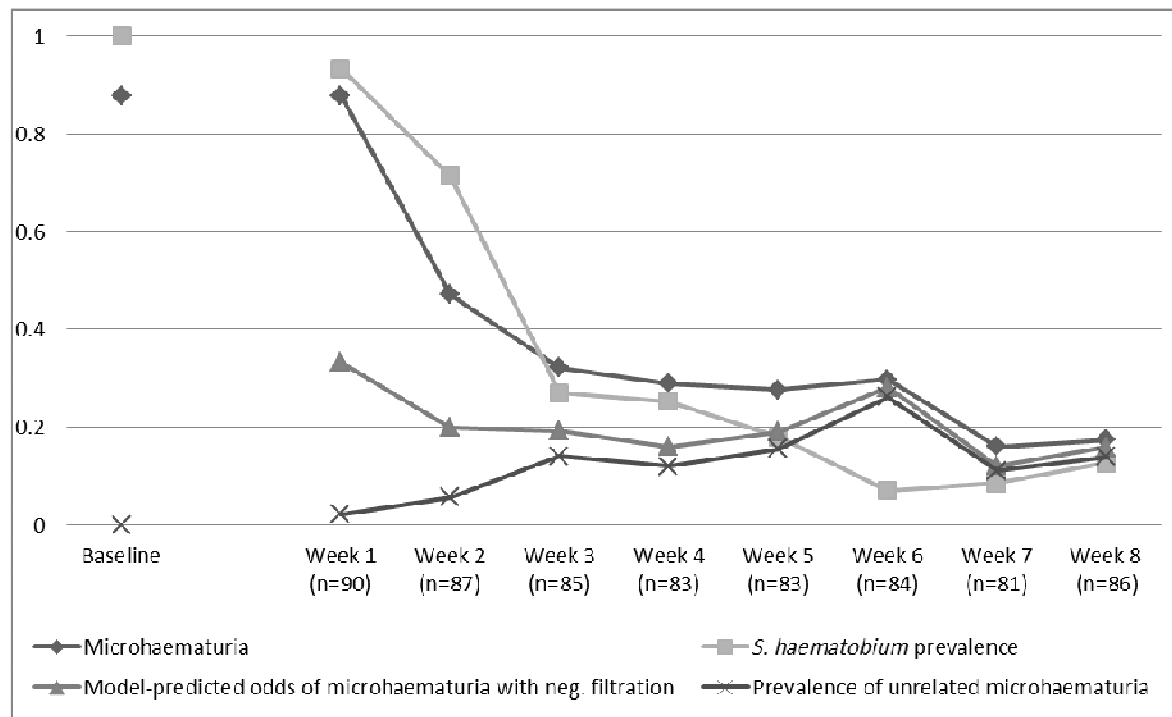


Figure 6.6 Dynamics of microhaematuria and model-predicted odds of microhaematuria unrelated to *S. haematobium* over an 8-week period post-treatment of all positive participants

Furthermore, our data indicate that this seemingly unrelated microhaematuria is mostly independent of gender. Although females consistently showed slightly higher levels of microhaematuria seemingly unrelated to *S. haematobium* than males in our studies from northern Côte d'Ivoire and Chad, this gender difference was only marginal over all age groups with the exception of women and men aged 45 years and above (Figure 5.7).

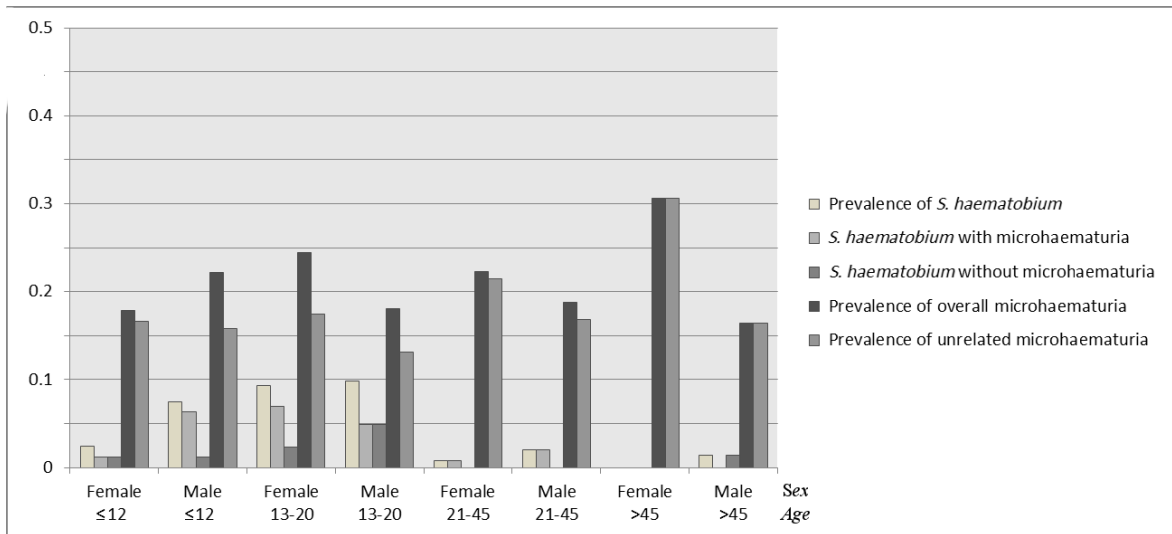


Figure 6.7 Unrelated microhaematuria, *S. haematobium* prevalence with and without associated microhaematuria and overall prevalence of microhaematuria by sex and age-group in northern Côte d'Ivoire and in the baseline survey in Chad.

6.4.4 Theoretical assessment of the likelihood of missed cases as explanation for seemingly unrelated microhaematuria

If we assume that all cases of “unrelated” microhaematuria can be explained by true *S. haematobium* cases that were missed with urine filtration, the expected prevalence of “unrelated” microhaematuria could be calculated as follows:

Expected true prevalence of *S. haematobium* times the probability to miss a remaining infection.

One way to control for the true prevalence is to consider post-treatment studies only. Yet, although it reduces infection intensity, treatment with praziquantel does not always cure an infected individual. Hence, we employed the following assumptions:

- ① 18% of treated individuals are not fully cured (Keiser et al., 2010);
- ② 20% of low intensity *S. haematobium* cases are missed by urine filtration (note, the 20% difference in case-detection stems from a single compared to triplicate urine filtrations in a lightly infected study group) (Kosinski et al., 2011); and
- ③ 5.7% *S. haematobium* cases present without microhaematuria (note, arithmetic mean of *S. haematobium* infections without microhaematuria from all post-treatment studies from the Cochrane review and our own data, excluding one study of the Cochrane review with an exceptionally high number of *S. haematobium* cases without microhaematuria).

The expected prevalence of “FP” reagent strips would consist of the uncured *S. haematobium* cases (presenting with microhaematuria) missed by urine filtration. Hence: ① + ② + (1-③) = $0.18 * 0.2 * (1-0.057) = 3.4\%$. The remaining “FP” reagent strip results cannot rationally be attributed to missed cases of *S. haematobium*.

If we assume that half of the treatments do not completely cure *S. haematobium* infections, the same rational would lead to an expected 9.4% ($0.2*0.5*(1-0.057)$) of seemingly unrelated microhaematuria which could be explained by missed *S. haematobium* cases. Re-infection can of course increase the prevalence of *S.*

haematobium after treatments. The level of re-infection in the included studies is unknown, but it is unlikely to change the numbers to a big extend.

6.5 Discussion

The current comparison of findings of *S. haematobium* eggs in urine and microhaematuria detected by reagent strips confirmed that the usefulness of microhaematuria as a proxy for estimating community prevalence of *S. haematobium* is influenced by the overall prevalence of *S. haematobium* (Lengeler et al., 1993; Birrie et al., 1995; Van Der Werf and De Vlas, 2004; Kosinski et al., 2011; King and Bertsch, 2013; Ochodo et al., 2015). The Kappa agreement between the two tests revealed very good agreement (>0.80). Moreover, the sensitivity and specificity of microhaematuria have repeatedly been found to be high enough for the reagent strip testing to be a valid diagnostic tool for *S. haematobium* at the community level. These parameters are considerably influenced by the association of *S. haematobium* infection with microhaematuria (94.3%). However, PPV was very low in low-prevalence settings indicating that either large fractions of microhaematuria in such settings are unrelated to schistosomiasis or that the true prevalence of *S. haematobium* in these settings is grossly underestimated. NPV and PPV are well known to be prevalence-dependent with lower PPV and higher NPV the lower the prevalence of the disease in a given setting (Altman and Bland, 1994; Heston, 2011). In this sense our findings on the NPV and PPV are not novel, yet, they imply that a positive reagent strip test would not necessarily relate to a positive *S. haematobium* result in very-low-prevalence settings.

Our findings have several implications that are offered for discussion. First, regardless of the study settings, there seems to be some level of “background microhaematuria”, which is, at first glance, not directly related to *S. haematobium* infection. The average level of this seemingly unrelated microhaematuria was around 13% across settings and reported *S. haematobium* prevalences. The observation that background microhaematuria tends to decline with higher prevalence of *S. haematobium* (visualized in Figure 5.5) can be explained by the

increasing probability to be infected with *S. haematobium*, which will hide any unrelated microhaematuria either because it is being attributed to schistosomiasis or because it co-occurs with *S. haematobium*-induced microhaematuria.

Some authors have argued that most of this background microhaematuria is due to undetected *S. haematobium* explained by the lack of sensitivity of widely used diagnostic tools (Bergquist et al., 2009; Utzinger et al., 2015). However, data from studies performed after praziquantel administration challenge this hypothesis. Indeed, after praziquantel administration, the number of seemingly unrelated microhaematuria attributable to missed *S. haematobium* cases consist of individuals for whom treatment failed to clear infection (or perhaps explained by the presence of immature *S. haematobium* flukes that are only marginally affected by praziquantel or the occurrence of rapid reinfection). If 20% of *S. haematobium* cases are missed by urine filtration (Kosinski et al., 2011) and 18% of positive *S. haematobium* cases treated with praziquantel are not fully cured (Keiser et al., 2010) and 5.7% of *S. haematobium* infections present without microhaematuria, only 3.4% ($0.18 * 0.2 * (1 - 0.057)$) of seemingly unrelated microhaematuria cases would be attributable to missed cases in post-treatment studies. The remaining unrelated microhaematuria of, say at least 10%, would remain unexplained and further studies are warranted to assess the cause of this microhaematuria. Potential aetiologies include bladder-stones or urinary tract infections and sickle cell disease as well as persistent bladder lesions from cured *S. haematobium* infections (Benbassat et al., 1996; Tomson and Porter, 2002; McDonald et al., 2006). Truly FP reagent strip results have also been reported, and are thought to be caused by the presence of semen in urine (Mazouz and Almagor, 2003). However, some studies suggest that cure rates of *S. haematobium* infections after praziquantel vary greatly depending on the study and the diagnostic effort and can be as low as 50% (King et al., 2000; Liu et al., 2011) which would indicate that the majority of the background microhaematuria that we found throughout settings would indeed be explained by *S. haematobium* infections missed by urine filtration. If this assessment holds, it would mean that there is a persisting *S. haematobium* prevalence of around 10-15% in settings which were characterised to have lower prevalences. In turn, this would change the current

picture about schistosomiasis burden of disease as well as the evaluation of the success of schistosomiasis control programmes. Indeed, a recent study on a promising high-sensitivity diagnostic tool based on the detection of a circulating anodic antigen (UCAA) did find a prevalence of 13.3% of *S. haematobium* with the antigen test when urine filtration found a prevalence of only 3.3% and reagent strip testing found a prevalence of 4.1% (Knopp et al., 2015).

Due to the lack of a 'gold' standard in *S. haematobium* diagnosis, it cannot be ascertained 100% whether this background haematuria results from missed *S. haematobium* cases or from alternative causes of microhaematuria. The level of seemingly unrelated microhaematuria did not differ much between males and females for different age groups, excluding the explanation of unrelated microhaematuria caused by pregnancy or menstruation. If the observed background haematuria is due to different aetiologies, such as bladder-stones or urinary tract infections it follows that individual treatment-decisions targeting *S. haematobium* should not merely be based on reagent strip results, particularly in low-prevalence settings.

In either case, researchers, health care personnel and disease control managers need to be aware that in settings with a *S. haematobium* prevalence below 20%, especially in settings targeted for elimination, a positive reagent strip test should always be followed up with urine filtration or better with other, more sensitive, diagnostic assays. And in view of the likelihood to miss an infection, which is, in addition, higher in low-intensity infections, and the fact that egg output shows a considerable day-to-day fluctuation (Lengeler et al., 1993; Lwambo et al., 1997; Vinkeles Melchers et al., 2014), the follow-up diagnosis should contain multiple samples over consecutive days.

Taken together, while reagent strip testing remains a valid tool for the overall assessment of community prevalence of *S. haematobium* (Lengeler et al., 1993; Mtasiwa et al., 1996; Robinson et al., 2009) or even for individual diagnosis (Mott et al., 1985a; Taylor et al., 1990; Ochodo et al., 2015), one has to consider the epidemiological setting in which the test is executed as well as the goals of a schistosomiasis control or research programme.

Praziquantel is a safe and efficacious drug that is recommended for preventive chemotherapy against schistosomiasis (WHO, 2002b; Knopp et al., 2013). Yet, as preventive chemotherapy is escalating and schistosomiasis elimination is the new goal (WHO, 2012c; Rollinson et al., 2013b), the proportion of people uninfected who will be given praziquantel is increasing and the repeated treatment of uninfected individuals might result in declining coverage rates.

6.6 Conclusion

Irrespective of the true cause of the persisting background prevalence of microhaematuria – be it missed *S. haematobium* cases or alternate causes for microhaematuria – the overwhelming implication of our findings and those of other researchers, is that there is a need for more accurate diagnostic tools (higher sensitivity and higher specificity) if we indeed want to aim for elimination of schistosomiasis in selected settings (Knopp et al., 2013; Rollinson et al., 2013b; Knopp et al., 2015; Utzinger et al., 2015). New research and funding efforts should target the well-known weaknesses of currently available diagnostic assays for urogenital schistosomiasis.

6.7 Acknowledgements

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7. Validation of a point-of-care circulating cathodic antigen urine test for *Schistosoma mansoni* diagnosis in the Sahel, and potential cross-reaction with pregnancy

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7.1 Abstract

On the shores of Lake Chad, schistosomiasis among mobile pastoralists was investigated in a field laboratory. Point-of-care circulating cathodic antigen (POC-CCA) cassette test, reagent strips, and filtration were conducted on urine samples. Fresh stool samples were subjected to the Kato-Katz technique, while fixed samples were examined with an ether-concentration method at a reference laboratory. POC-CCA urine cassette tests revealed a *Schistosoma mansoni* prevalence of 6.9%, compared to only 0.5% by stool microscopy. Four pregnant women with negative coprology had positive POC-CCA. This result raises concern of cross-reactivity due to pregnancy. Hence, two pregnant women in Switzerland with no history of schistosomiasis were subjected to POC-CCA and there was one positive test result. Our data suggest that POC-CCA can be performed under extreme Sahelian conditions (e.g., temperatures >40°C), and it is more sensitive than stool microscopy for *S. mansoni* diagnosis. However, potential cross-reactivity in pregnancy needs further investigation.

7.2 Introduction

Schistosomiasis is listed among the neglected tropical diseases (NTDs) (Hotez et al., 2014b) and specifically mentioned in the World Health Assembly resolution WHA 65.21a that calls for global elimination by 2025.(2013) In Africa, schistosomiasis is mainly caused by chronic infection with *Schistosoma haematobium* and *Schistosoma mansoni* (Colley et al., 2014). The most widely used diagnostic approaches for *S. haematobium* are urine filtration with microscopy and reagent strip testing for microhaematuria, whereas the diagnosis of *S. mansoni* heavily relies on Kato-Katz thick smear examination under a microscope (Utzing et al., 2015). In rural areas of Africa, where most of the worldwide *Schistosoma* infections occur, the capacity of health centres is insufficient to provide even these basic laboratory diagnostics. Hence, the World Health Organization (WHO)'s plan for global elimination of schistosomiasis will require additional diagnostic tools, characterized by high sensitivity, high specificity, and ease of use at the point-of-care (POC), and low costs (Utzing et al., 2015). First products developed within this spirit are already available on the market. One of them is a POC circulating cathodic antigen (CCA) urine cassette test for the diagnosis of *S. mansoni*. Indeed, the POC-CCA urine cassette test has been successfully validated in a multi-country study (Colley et al., 2013) and is being recommended by WHO for the rapid mapping of community prevalence in endemic settings(Utzing et al., 2015), and might be utilized for rapid diagnosis of African migrants and returning travellers to Europe (Becker et al., 2015).

With regard to the WHO goal of schistosomiasis elimination, it is important to gain a deeper insight into the disease situation in endemic areas. In Chad, nationwide data on schistosomiasis date back to the 1970s.(Becquet et al., 1970; Delpy et al., 1972) More recent studies reflect the infection status of the urban population in the vicinity of the capital city of N'Djamena (Massenet et al., 1995; Hamit et al., 2008; Massenet et al., 2012; Moser et al., 2014). Yet, to attempt elimination, a more detailed picture of the infection status in the rural Chadian population is required and specific at-risk groups must be identified.

Here, we report findings from a cross-sectional survey among mobile pastoralists from the Lake Chad region, placing particular emphasis on the use of the POC-CCA urine cassette test under extreme environmental conditions (e.g., aridness and air temperature up to 48°C). Our findings are compared to the standard Kato-Katz technique and an ether-concentration method of fixed stool samples for *S. mansoni* diagnosis. As we found a potential cross-reaction of the POC-CCA test among pregnant women, we invited two pregnant women from Switzerland with no history of schistosomiasis to participate

7.3 Materials and Methods

7.3.1 Ethics statement

The validation of the POC-CCA urine cassette test for the diagnosis of *S. mansoni* was embedded in a larger epidemiologic study pertaining to helminth infections in mobile pastoralists and their livestock in the Lake Chad area in eastern Chad. The study was approved by the ethics committee in Basel, Switzerland (EKBB; reference no. 64/13). In Chad, research permission, including ethical approval, was obtained from the 'Direction Générale des Activités Sanitaires' (reference no. 343/MSP/SE/SG/DGAS/2013). The aim and procedures of the study were explained to each group of mobile pastoralists. Informed consent was signed by the group leader after discussion within the group. Due to high illiteracy rates, randomly selected individuals within each group provided oral consent. All participants found with a positive test result for *S. haematobium* by urine filtration and *S. mansoni* on the spot (Kato-Katz thick smear and POC-CCA urine cassette test) were treated with a single 40 mg/kg oral dose of praziquantel (2002).

7.3.2 Procedures

The data were collected between April and May 2014 in 13 camps of mobile pastoralists on the south-eastern shores of Lake Chad. A mobile field laboratory was set up in the shade of a tree in close proximity to camps. Study participants were given two collection containers; one for urine and one for stool. Urine samples were

collected between 10 a.m. and 9 p.m., with 60% of urine samples collected between 10 a.m. and 2 p.m. Urine samples were first tested for microhaematuria, a proxy for *S. haematobium* infection (Savioli et al., 1990a), using reagent strips (Hemastix, Siemens Healthcare Diagnostics GmbH; Eschborn, Germany). Second, a POC-CCA cassette test (Rapid Medical Diagnostics; Pretoria, South Africa) was employed for *S. mansoni* diagnosis. Third, 10 mL of urine were filtered using a syringe pressed through a 13-mm diameter filter holder containing a 20 µm wire-mesh filter (Sefar AG; Heiden, Switzerland). Filters were examined under a solar-empowered light microscope by a trained laboratory technician and the first author.

From each stool sample, a single Kato-Katz thick smear using 41.7 mg standard templates was prepared and examined under a microscope on the spot by a trained laboratory technician (Katz et al., 1972b). Additionally, approximately 1 g of stool was fixed in a Falcon tube containing 20 mL of sodium acetate-acetic acid-formalin (SAF). The SAF-fixed stool samples were forwarded to the Swiss National Reference Laboratory for Imported Parasitic Infections at the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland) and subjected to an ether-concentration method for the diagnosis of *S. mansoni* and other helminths (Uttinger et al., 2010).

7.4 Results

Urine and stool samples were obtained from a random sample of 193 individuals in 13 mobile camps. Complete parasitological data (i.e., reagent strip, urine filtration, POC-CCA cassette test, Kato-Katz thick smear, and SAF-fixed stool samples examined by an ether-concentration technique) were available from 187 participants (96 females, 91 males). There were 13 positive POC-CCA urine cassette tests, owing to a *S. mansoni* prevalence of 6.9%. Stool microscopy, using Kato-Katz and ether-concentration, detected eggs of *S. mansoni* in only one individual (0.5%). There were more than twice as many positive POC-CCA urine cassette tests in females (n=9) compared to males (n=4), whereas the only positive stool microscopy was in a male participant. Among the 13 positive POC-CCA urine cassette tests, 8

showed a faintly positive test line, whereas the remaining 5 showed a strong positive test line (Figure 6.1) (Coulibaly et al., 2013a).

According to the manufacturer's guidelines for the POC-CCA assay, the intensity of the test line is correlated with the intensity of *S. mansoni* infection. It is also mentioned in the guidelines that heavy infections with *S. haematobium* and microhaematuria may produce (false-) positive test results in the POC-CCA cassette test. Positive reagent strip or urine filtration results were present in all 4 male participants who were POC-CCA cassette test positive, but coprology-negative. In females, on the other hand, 6 Individuals with positive POC-CCA cassette tests were found negative with all other tests employed (Kato-Katz, ether concentration, reagent strip, and urine filtration) (Table 1).

Those six females who had a positive POC-CCA that could not be explained due to a *S. haematobium* infection or microhaematuria were adults at reproductive age (19-39 years). We found that 3 out of the 6 women were pregnant (Table 2). For all pregnant women, POC-CCA urine cassette tests were repeated and positive tests were confirmed.

The aforementioned positive POC-CCA urine cassette test results, coupled with negative coprological examinations, raises concern about a potential cross-reaction of POC-CCA in pregnancy. Hence, two pregnant women from Switzerland without any history of exposure to schistosomiasis-endemic countries voluntarily agreed to provide urine samples that were subjected to duplicate POC-CCA urine cassette testing. In one of the two pregnant women, the POC-CCA consistently revealed a faintly positive test line (Figure 6.1).

Table 7.1 Comparison between positive POC-CCA urine cassette tests and stool microscopy, urine filtration, and reagent strips (total number and stratified by sex)

	Overall	Males	Females
POC-CCA urine cassette test positive	13	4	9
<i>S. mansoni</i> egg-positive (Kato-Katz and/or ether-concentration)	1	1	0
<i>S. haematobium</i> egg-positive (urine filtration) and microhaematuria positive (reagent strip)	3	2	1
Microhaematuria positive (reagent strip) and <i>S. haematobium</i> egg-negative (urine filtration)	3	1	2
POC-CCA urine cassette test positive alone	6	0	6

Table 7.2 Comparison between positive POC-CCA urine cassette test, stool microscopy, urine filtration, and reagent strip results for female participants, stratified by age group and pregnancy status.

For the category “females, > 14 years” pregnancy status was not assessed

	Females, all ages	Females, <14 years	Females, >14 years	Females, >14 years and pregnant
POC-CCA urine cassette test positive	9	1	4	4
<i>S. mansoni</i> egg-positive (Kato-Katz and/or ether-concentration)	0	0	0	0
<i>S. haematobium</i> egg-positive (urine filtration) and microhaematuria positive (reagent strip)	1	0	1	0
Microhaematuria positive (reagent strip) and <i>S. haematobium</i> egg-negative (urine filtration)	2	1	0	1
POC-CCA urine cassette test positive alone	6	0	3	3

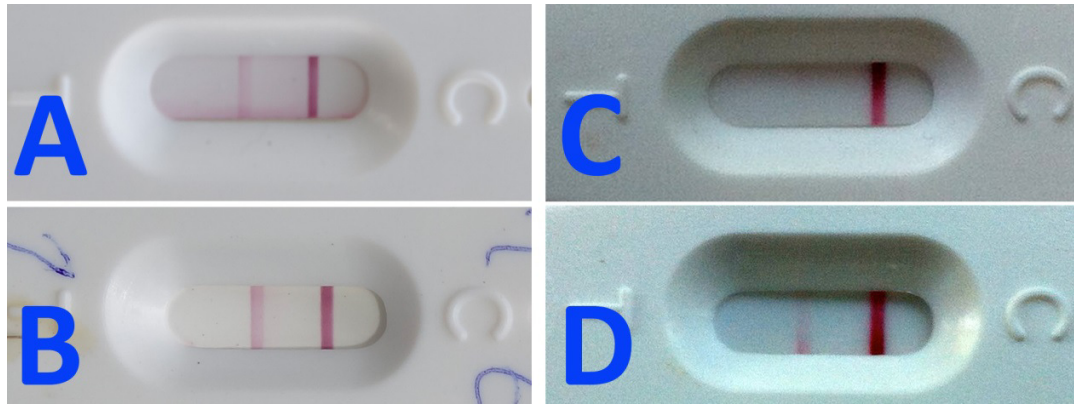


Figure 7.1 Point-of-Care Circulating Cathodic Antigen (POC-CCA) urine cassette test results obtained from samples in Chad

(A, B) and from pregnant women in Switzerland (C, D).

A, faintly positive test band from Chad

B, strong positive test band from Chad

C, negative test result from Swiss pregnant woman

D, positive test result from Swiss pregnant woman

7.5 Discussion

POC-CCA urine cassette tests were employed among 193 mobile pastoralists, aged 5-77 years, under extreme environmental conditions in Chad. In contrast, most of the previously published studies that validated the POC-CCA urine cassette test for diagnosis of *S. mansoni* in schistosomiasis-endemic areas focused on school-aged children (van Dam et al., 2004b; Stothard et al., 2006; Legesse and Erko, 2007; Ayele et al., 2008; Midzi et al., 2009; Coulibaly et al., 2011; Tchuem Tchuente et al., 2012; Adriko et al., 2014; Foo et al., 2015; Mwinzi et al., 2015). Positive POC-CCA urine cassette test results in males and females with negative stool microscopy may be explained by the fact that we only examined a single stool sample per participant, and hence, we might have missed individuals with low infection intensity (Utzinger et al., 2001b). Interestingly, we found a considerable number of positive POC-CCA urine cassette tests among pregnant women with negative stool microscopy. These results were confirmed when repeating POC-CCA urine cassette tests. Moreover, one of two pregnant women in Switzerland without history of schistosomiasis exposure had a positive POC-CCA result. Hence, our results raise concern about a potential cross-reaction with certain non-*Schistosoma*-related metabolites in pregnant women's urine. These observations warrant further research to assess the reliability and accuracy of POC-CCA urine cassette tests before wider health care practice.

Treatment with praziquantel – be it in the frame of preventive chemotherapy or targeted to positive individuals – is safe (Utzinger and Keiser, 2004a) and, WHO guidelines established in 2002, explicitly recommend its administration also to pregnant or lactating women (Allen et al., 2002). Yet, most guidelines discourage intake of medicines during pregnancy to minimize risk of adverse events. In the endgame of reaching the ultimate goal of schistosomiasis elimination, a test-and-treat strategy is likely to gain traction. It will be important to dispose of rapid, easy-to-handle diagnostic tools at the POC that are highly accurate, e and whose performance remains reliable even under extreme environmental conditions such as in the Sahel.

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8. Access to, and use of, water by populations living in a schistosomiasis and fascioliasis co-endemic area of northern Côte d'Ivoire

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8.1 Abstract

Water is an essential element of life, but it can also be a source of disease. Apart from direct consumption of unsafe water, direct contact and indirect consumption puts people at risk of many different types of pathogens. Employing a mixed methods approach, consisting of questionnaires and direct observations, we assessed access to, and use of, different water sources by the participants of the district des Savanes in northern Côte d'Ivoire. The use of water sources was put in relation to the potential risk of acquiring schistosomiasis and fascioliasis. Overall, 489 people aged 8 to 82 years participated. While all participants had access to safe water, 63% were in direct contact with unimproved water and 31% directly consumed unsafe water. More than a third of the people who otherwise reported using only improved water for all activities came in contact with unimproved water through crossing open water when going to their workplace, school or other destinations. Self-reported blood in urine – a marker for *Schistosoma haematobium* with reasonable sensitivity and specificity– was reported by 6% (n=30), self-reported blood in stool – an unspecific marker for *Schistosoma mansoni* – was reported by 7% (n=35), while blood co-occurring in both urine and stool was reported by another 10% (n=48) of participants. Accessing unimproved water for any activity (including crossing) was associated with higher odds of reporting blood in urine and/or blood in stool (odds ratio: 1.90; 95% confidence interval: 1.07-3.36). Our results have important ramifications for intervention programmes targeting neglected tropical diseases, and emphasise the need for a wider supply of safe water to rural populations, since the water supply at the workplace needs to be considered as well next to the water supply at home. Crossing of open water sources is an important risk factor for sustained transmission of schistosomiasis.

Keywords: Côte d'Ivoire; direct observation; fascioliasis; questionnaire; schistosomiasis; water contact

8.2 Introduction

Water is an indispensable source of life, yet it can also be a source of disease (Fenwick, 2006; Steinmann et al., 2006a; Traore et al., 2013). A plethora of bacteria, parasites, protozoa and viruses are transmitted via water. Water-borne diseases mostly affect communities who lack access to clean water and adequate sanitation and have substandard hygiene, often in a context of resource-constrained health systems (Brunn and Aagaard-Hansen, 2008; Utzinger et al., 2009b; Bartram and Cairncross, 2010). When it comes to the prevention of poverty-related diseases, supply with safe water is paramount (Fewtrell and Colford, 2005; Grimes et al., 2014; Strunz et al., 2014). Apart from direct consumption of unsafe water, indirect consumption through plants that grow in water or were irrigated with unsafe water puts people at risk as well (Drechsel et al., 2010). Human fascioliasis, for example, is acquired through the ingestion of the parasite encysted on freshwater plants or lettuce irrigated with contaminated water, but also through drinking contaminated water or even using utensils washed with contaminated water (Curtale et al., 2003; Marcos et al., 2005; Matthys et al., 2007). Furthermore, even the mere contact with unsafe water during agricultural, domestic and recreational activities puts people at risk for diseases such as schistosomiasis (Sama and Ratard, 1994; Brunn and Aagaard-Hansen, 2008).

In the district des Savanes of northern Côte d'Ivoire, water is widely distributed. Many rivers and small water bodies can be found in the area all throughout the year, although some of the small water bodies carry less water or dry out completely during the dry season (Cecchi, 1998; Koné, 2009). Large governmental efforts in the 1970s led to the construction of hundreds of small, multi-purpose dams (Cecchi, 1998). These man-made dams were primarily intended to foster livestock rearing but have long since been repurposed to all kinds of activities, most notably for irrigation of crops and vegetables (Hunter et al., 1993). Yet, next to its positive aspects, water resources development and management can also create new habitats for snails and new mosquito breeding sites, and hence, constitute potential transmission sites for several diseases including, but not limited to, schistosomiasis, malaria,

fascioliasis and other food-borne trematodiasis and lymphatic filariasis (Hunter et al., 1993; Keiser and Utzinger, 2005a; Fenwick, 2006; Steinmann et al., 2006a). It follows that, while access to improved water in the villages and cities can reduce disease exposure to some extent (Fewtrell and Colford, 2005), the nature of life in sub-Saharan Africa renders this more difficult for specific diseases (Hunter et al., 2010). Therefore, access to, and use of, different water sources in a specific eco-epidemiological setting have to be considered for public health interventions.

A recent national survey, coupled with geospatial analysis, revealed that the prevalence of schistosomiasis in the district des Savannes ranges between 1 and 5% (Chammartin et al., 2014). The prevalence of animal fascioliasis in this part of Côte d'Ivoire is estimated to be around 12% in sheep and goats and 4% in cattle (Achi et al., 2003b; Achi et al., 2003e).

The purpose of this study was to deepen our understanding of access to, and use of, different water sources by the population of the district des Savanes, northern Côte d'Ivoire. Our aim was to gather knowledge about the availability of different improved and unimproved water sources in the area, the various activities performed at specific water sites and to understand why water is being used the way it is. Furthermore, we related the use of water to the potential risk of acquiring schistosomiasis and fascioliasis, as assessed through reported blood in urine and/or reported blood in stool, as well as the consumption of potentially infected water and plants.

8.3 Materials and Methods

8.3.1 Ethics statement

The study protocol was approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland). Ethical approval was granted by the ethics committees of Basel (reference no. EKBB 64/13) and Côte d'Ivoire (reference no. 32-MSLS/CNERdkn). District health and village authorities, study participants and parents/guardians of individuals aged <18 years were informed about the purpose and procedures of the study, including potential risks and benefits. It was emphasised that participation was voluntary and people

could withdraw from the study at any time without further obligation. Written informed consent was obtained from participants or the parents/guardians of minors before the start of the interviews. All results were coded and treated confidentially.

8.3.2 Study area and population

The study was carried out in 10 randomly selected villages within the district des Savanes in northern Côte d'Ivoire. All study villages lie between 3 and 113 km radial distance from the district's capital Korhogo, which is situated approximately 660 km north of Abidjan, the economic capital of Côte d'Ivoire. The northern part of Côte d'Ivoire is characterised by a Sudano-Guinean climate with a single rainy season that lasts from June to October. The average annual precipitation ranges between 800 and 1,400 mm (FAO, 2009). The dry season spans over a 6-month period from November to May with a desiccating, dust-carrying Sahara wind (Harmattan) between November and February. This Harmattan period is marked by cold nights, hot days and very low humidity and is followed by an upsurge in temperature from the end of February to mid-May (MPARH, 2003). The mean temperature is 25°C during the rainy season and 28°C during the dry season (Aka et al., 2000).

The ecology of northern Côte d'Ivoire is characterised by mostly semi-arid soil interspersed by many small rivers draining from North to South, small water bodies that often drain during dry season and small dams that had been constructed in the 1970s (Cecchi, 1998). The prevailing ethnic groups of the study area are the Senoufo and members of the semi-nomadic Peulh population, also known as Fulani. For the purpose of this study, only the sedentary villagers have been considered.

8.3.3 Selection of villages and households and questionnaire survey

Fieldwork for this study was conducted in the month of December 2013 employing a mixed methods approach consisting of questionnaires and direct observations. In a first step, 10 villages were randomly selected. A readily available list of all primary schools of the district des Savanes was used for this purpose. The villages were selected by generating a corresponding set of random numbers using

the online application Research Randomizer Version 4.0 (Urbaniak and Plous, 2013).

Within the selected villages, local authorities were informed and then 12-18 households were selected in each village using a method adapted from the Extended Programme of Immunization (EPI) described elsewhere (Henderson and Sundaresan, 1982b). In brief, starting from the village centre, as defined by a village authority, a geographical direction was randomly determined for each investigator by turning a pen. Subsequently a paper lot numbered from 1 to 20 was drawn and settlements on each side of the path were counted and the drawn number was then sampled. In case a selected house was unoccupied, the neighbouring house was selected instead. For subsequent houses, the procedure was repeated and counting started from the last sampled house and in the original direction. Within each household, two to four people were invited to participate. Wherever possible, two adults and two children (<15 years of age) of both genders were encouraged to participate in each household.

After participants gave their written informed consent, they were interviewed with a pre-tested questionnaire pertaining to water use patterns related to everyday activities as well as self-reported blood in urine and stool. Questionnaires were administered as an interview held in either French, the official national language, or one of the two most common vernacular languages in the district des Savanes, namely Dioula (similar to Malinke and Bambara) and Senufo, or in a combination of these languages. All investigators had received a 3-day training on questionnaire-based interviews, methods, practices and underlying ethical considerations. Interviews were performed from 8 a.m. to 5 p.m.

8.3.4 Direct observation

In a second part of the study, water bodies, habitually frequented by people and domestic animals in and around the villages, were visited by the study team accompanied by 1-2 locals with an informed consent. During these visits, the accompanying locals were asked a list of questions pertaining to water-related

activities frequently performed at the visited site by themselves and their fellow villagers. Questions were asked in a conversational manner. Additionally, photos from each site and the geographical coordinates of the water bodies were taken using a hand-held global positioning system (GPS) receiver (Garmin eTrex 10; Garmin LTD, Kansas, USA). The presence of ruminants or tracks thereof in and around the water bodies was recorded likewise in order to assess the potential risk for acquiring zoonotic diseases at the water source.

8.3.5 Proxies for *Schistosoma* infection

Self-reported blood in urine was used as a marker for *Schistosoma haematobium*, whereas self-reported blood in stool, an unspecific yet important symptom in intestinal schistosomiasis was used as a rough proxy for *Schistosoma mansoni* (Lengeler et al., 2002b).

8.3.6 Statistical analysis

Data were double-entered into EpiInfo™ version 7.0 (Centers for Disease Control and Prevention; Atlanta, USA), checked for internal consistency and analysed with R version 3.1.0 (Center for Statistics; Copenhagen; Denmark) and Stata/IC version 12.1 (StataCorp; Texas, USA). All completed questionnaires were included in the final analysis. Age was grouped as follows: (i) 8-15, (ii) 16-39 and (iii) ≥ 40 years. A random effects logistic regression model with village as random effect was performed to assess the relationship between reported blood in urine and/or reported blood in stool and water use.

8.4 Results

8.4.1 Study population

Interviews were performed with 489 individuals aged 8-82 years (median 28 years, 57% females) from 151 households. The interviews were held in Senufo (45%), Dioula (18%) and French (10%), while in 27% of the interviews a combination of two

or three languages was used. The most common professional occupation of the study participants was farming (41.1%), followed by housekeeping (11.9%), studying (10.8%) and commerce (8.8%). About one out of six interviewees (17.8%) reported to be unemployed. Working in agriculture was reported by two thirds of the study participants (n=330, 67.5%). Many school-aged children do also work on the fields, particularly during the main harvesting season (n=20, 40%). Additionally, children often worked as herders, either on their school-free day or instead of going to school.

8.4.2 Water contact pattern

Access to, and use of, water sources

Unimproved water sources, such as slow-flowing rivers (6 villages), small pond-like water bodies known as “marigots” (6 villages), man-made dams (5 villages), seasonal swamps (3 villages) and poorly protected wells in the bush (1 village), were at a mean distance of 1.9 km (range 0.2-5.6 km) from the border of the villages.

All study participants (n=489) reported to have access to and reported using improved water sources in the form of wells, public pumps, tap water or bottled water for at least some of their activities. Nevertheless, unimproved water sources were frequently accessed by at least some individuals from all villages. Overall, 63% of study participants reported accessing and using unimproved sources during the 2 months prior to the study (Fig. 1).

Water contact was reported for various general purposes such as consumption (preparing food and direct consumption), hygiene and religion (body hygiene, toilet and religious cleaning), cleaning (clothes, dishes, house, etc.), professional activity (irrigation, fishing and maintenance), recreation (playing, swimming and bathing) and crossing water.

Water destined for consumption (preparing food and drinking combined) was taken from only improved water sources by two thirds of the population (68%). The remaining 32% of people interviewed reported to simultaneously also consume water from unimproved sources and to drink it without prior treatment.

Other water-related activities, such as hygiene and cleaning, were also commonly reported; 79-82% of people reported only using improved sources, compared to 18-21% who reported using a combination of both or only unimproved water. An exception constitutes water contact during professional activities such as maintenance of a source, fishing or irrigation. Of all participants reporting to contact water for occupational purposes (n=163), almost half of this contact (44%) was with unimproved water sources. Water contact for recreational purposes was mainly performed using unimproved water (87%), and was predominantly reported by participants below the age of 18 years (95% of all who reported water contact for recreational purposes).

The exact use of improved and unimproved water sources, stratified by activity, is summarised in table 7.1. When grouped together for all activities, 62% (n=305) of the participants exclusively used improved water for their everyday activities, whereas 38% (n=184) used a combination of unimproved and improved water and none used unimproved water exclusively. All participants reported using improved water for at least some of their daily activities.

The need for crossing open water changed the participant's water contact patterns. A total of 52% (n=256) of participants reported to have been crossing open water during the 2 months prior to the interview. Furthermore, of 305 participants who otherwise reported to only use improved water sources, 117 (38%) were obliged to contact open water in order to reach their workplace, school or other destinations (Fig. 1).

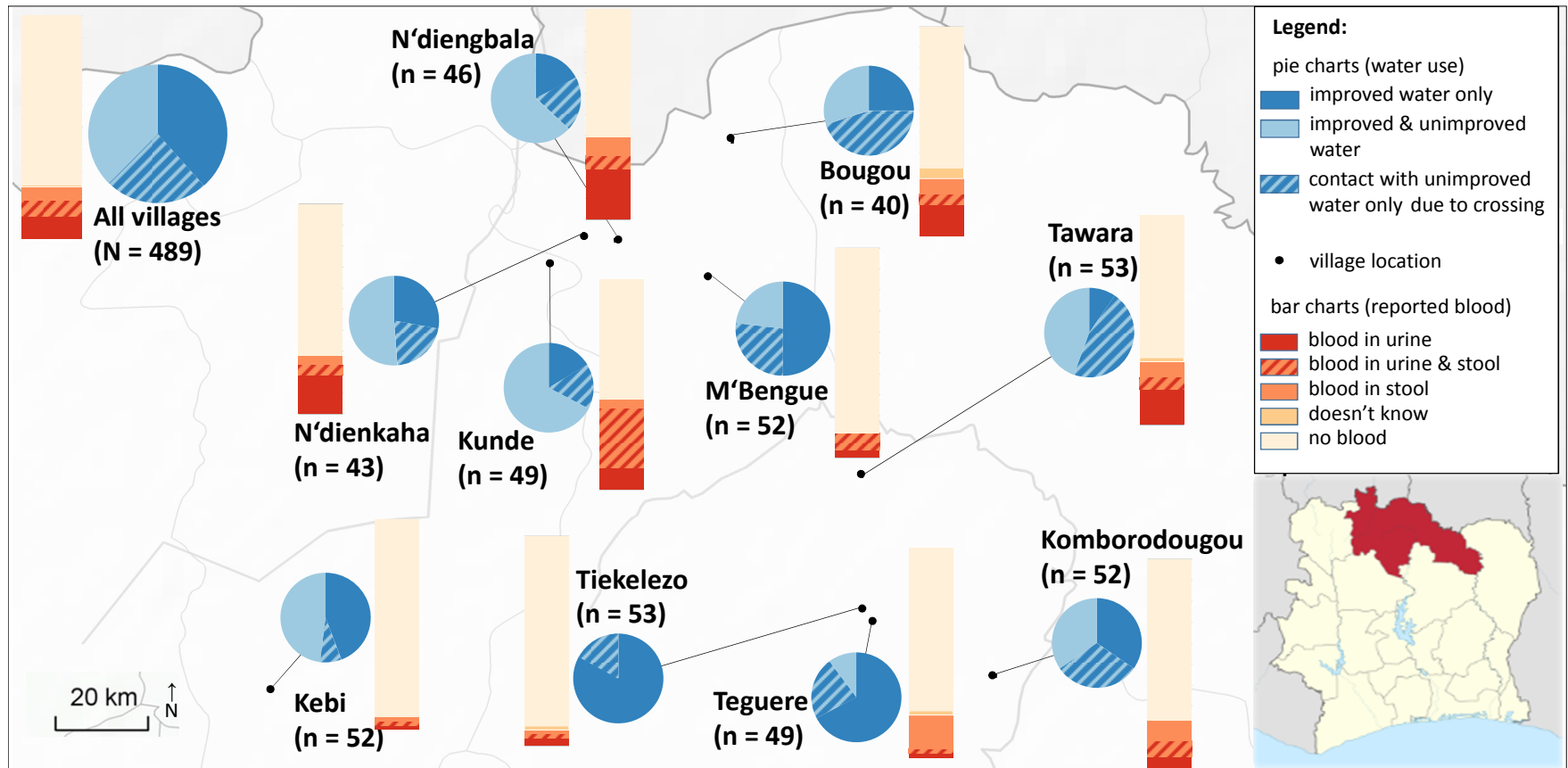


Figure 8.1 Village location, use of improved water and reported blood stratified by villages

Table 8.1 Use of improved and unimproved water by activity (percentage of all who reported the activity)

Activity	Only improved	Improved + unimproved	Only unimproved	Total reported
Drinking	338 (69%)	150 (31%)	1 (0.2%)	489 (100%)
Cooking	422 (91%)	40 (9%)	1 (0.2%)	463 (95%)
<i>Consumption total</i>	334 (68%)	155 (32%)	0	489 (100%)
Dishwashing	275 (90%)	31 (10%)	0	306 (63%)
Laundry	314 (81%)	63 (16%)	9 (2%)	386 (79%)
Clean house	9 (100%)	0	0	9 (2%)
<i>Cleaning total</i>	313 (79%)	80 (20%)	5 (1%)	398 (81%)
Body hygiene	400 (83%)	76 (16%)	5 (1%)	481 (98%)
Toilet	285 (88%)	37 (11%)	3 (1%)	325 (66%)
Religious ritual	7 (88%)	0	1 (12%)	8 (2%)
<i>Hygiene and religion total</i>	395 (82%)	83 (17%)	5 (1%)	483 (99%)
Maintenance	99 (95%)	0	5 (5%)	104 (21%)
Fishing	--	--	65 (100%)	65 (13%)
Irrigation	0	0	5 (100%)	5 (1%)
<i>Professional activities total</i>	92 (57%)	7 (4%)	64 (39%)	163 (33%)
<i>Recreation</i>	8 (13%)	4 (6%)	51 (81%)	63 (13%)
All activities	305 (62%)	184 (38%)	0	489 (100%)
<i>Crossing water</i>	--	--	256 (100%)	256 (52%)
All activities + crossing	188 (38%)	301 (63%)	0	489 (100%)

8.4.3 Activities by water source

Tap water, pumps and wells were used more often for tasks usually performed at home (such as hygiene and cleaning purposes) than man-made dams, rivers and marigots. However, no clear attribution of water sources to different activities can be seen in the study population (Fig. 2). Recreational activities were almost exclusively performed in man-made dams, marigots and rivers. All water sources were used for consumption; however, water from man-made dams was consumed by a lower percentage (32%) of participants accessing these dams, compared to water from all other sources, which was consumed by nearly 100% of participants accessing these sources. Table 7.2 shows how everyday activities are distributed between the various water sources.

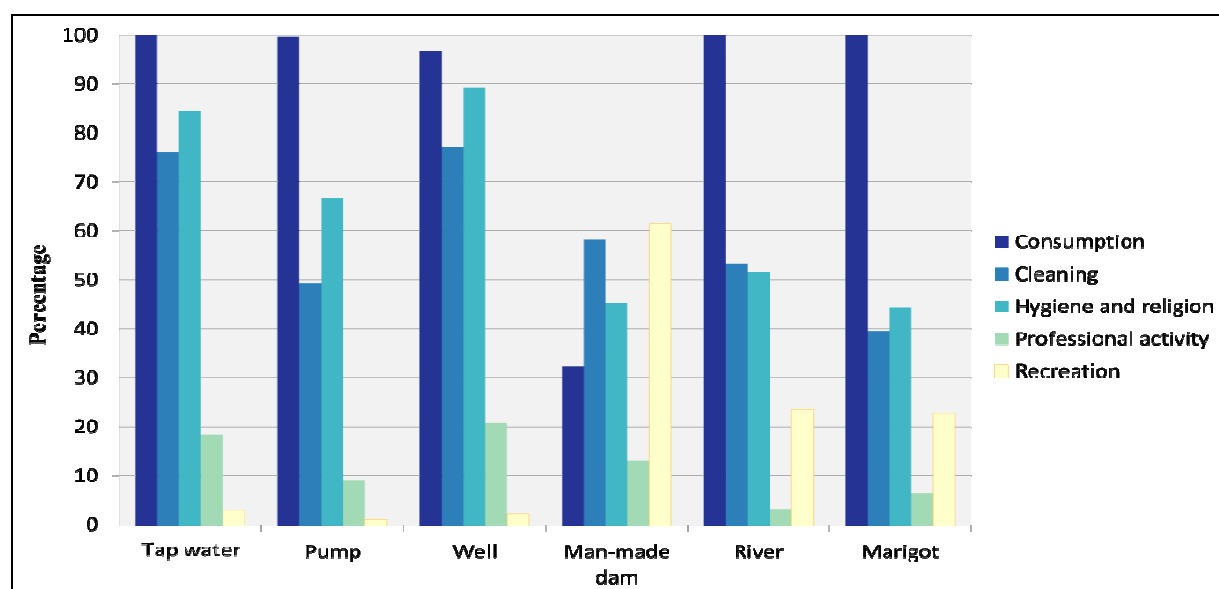


Figure 8.2 Water contact by categories and water source

Table 8.2 Activities performed at different water sources (percentage of all who reported using the source)

	Man-made					
	Tap water	Pump	Well	dam	River	Marigot
Use reported by (% of population)	71 (14.5%)	294 (60.1%)	382 (78.1%)	31 (6.3%)	64 (13.1%)	124 (25.4%)
Cooking (% of user)	50 (70.4%)	272 (92.5%)	225 (58.9%)	2 (6.5%)	23 (35.9%)	19 (15.3%)
Drinking (% of user)	69 (97.2%)	206 (70.1%)	361 (95.5%)	10 (32.3%)	52 (81.3%)	104 (83.9%)
<i>Consumption total (% of user)</i>	71 (100%)	293 (99.7%)	369 (96.6%)	10 (32.3%)	64 (100%)	124 (100%)
Dish washing (% of user)	44 (62.0%)	109 (37.1%)	216 (44.2%)	2 (0.4%)	19 (29.7%)	13 (10.5%)
Laundry (% of user)	51 (71.8%)	140 (47.6%)	277 (72.5%)	18 (58.1%)	26 (40.6%)	43 (34.7%)
Clean house (% of user)	3 (4.2%)	1 (0.3%)	5 (1.3%)	/	/	/
<i>Cleaning total (% of user)</i>	54 (76.1%)	145 (49.3%)	294 (77.0%)	18 (58.1%)	34 (53.1%)	49 (39.5%)
Body hygiene (% of user)	59 (83.1%)	195 (66.3%)	335 (87.7%)	12 (38.7%)	32 (50.0%)	50 (40.3%)
Toilet (% of user)	47 (66.2%)	117 (39.8%)	216 (56.5%)	2 (6.5%)	13 (20.3%)	26 (21.0%)
Religious ritual (% of user)	0 /	2 (0.7%)	5 (1.3%)	0 /	1 (1.6%)	0 /
<i>Hygiene and religion total (% of user)</i>	60 (84.5%)	196 (66.8%)	341 (89.3%)	14 (45.2%)	33 (51.6%)	55 (44.4%)
Maintaining/irrigation (% of user)	13 (18.3%)	26 (8.8%)	78 (20.4%)	1 (3.2%)	2 (3.1%)	7 (5.7%)
Fishing (% of user)	--	--	--	3 (9.7%)	0 /	1 (0.8%)
<i>Professional activity total (% of user)</i>	13 (18.3%)	26 (8.8%)	79 (20.7%)	4 (12.9%)	2 (3.1%)	8 (6.5%)
Recreation (% of user)	2 (2.8%)	3 (1.0%)	8 (2.1%)	19 (61.3%)	15 (23.4%)	28 (22.6%)

In grey are the summary variables created with the variables above that line. "Recreation" is a single and summary variable in and of itself

8.4.4 Reasons for the choice of water

When asked about the reasons for consuming water from unimproved sources, people stated that they often had no other choice than to drink or cook with water from open water bodies during work because no other water was available at their place of work and could also not be transported there. The same lack of choice plays a role in open defecation. During many visits of water sources, we were told that defecation and urination takes place close to the water or, in case of urination, even inside the water. Contrasting to people working on a field, people working in a big factory, such as the sugar factory near Ferkessedougou, are provided around 1 litre of drinking water per day per employee.

Another important consideration for the use of water were financial incentives. In Tiekelozo, for example, where tap water was widely available and used, people reported that they switch to using well or pump water whenever the water bill for tap water would get too high. Seasonal water scarcity due to dried out wells and costs were also stated as reasons why certain activities, such as washing clothes and irrigation, are generally not performed with improved water. Additionally, washing clothes was often considered a social activity during which women would meet, talk to each other and share news while doing their laundry. Accompanying children would then often play in the water where the mothers were washing clothes. Especially children herding and watering cattle, likewise reported swimming in the same source where cattle herds are being watered. Participants sometimes also mentioned that some water sources were preferred over other sources for certain tasks. The reasons for this varied from one village to another. The current of the river, for example, floats away the soap that is washed out of the clothes during the rinsing process and thus speeds up the rinsing while, at the same time, avoiding the need for frequent change. Other, more local reasons for such preferences were accessibility (a steep border would render it hard and even dangerous to wash clothes), perceived cleanliness and social norms (village habits and informal rules). In one village it was, for example, forbidden to use water for washing clothes at a location where groundwater emerged to the surface. However, these norms and

rules are highly setting-specific and differ not only between villages but also between different groups of people accessing these water sources. Members of nearby Peulh-camps or inhabitants of other villages accessing the same sources might therefore have different reasons and norms concerning their available water sources.

8.4.5 Factors pertaining to potential risk for schistosomiasis and fascioliasis

The overall rate of reported blood in urine and/or reported blood in stool during the 2 weeks prior to the interview was 23% (n=113). Blood in urine alone was reported by 6% (n=30), blood co-occurring in urine and stool by 10% (n=48), and blood in stool alone by 7% (n=35) (Fig. 1). The prevalence of reported blood in urine and/or reported blood in stool was significantly higher in participants below the age of 15 years compared to older counterparts (odds ratio (OR) 2.41; 95% confidence interval (CI): 1.45-4.00). Participants below 15 years of age were also more likely to access unimproved water compared to older participants (OR: 3.31; 95% CI: 1.81-6.04). Gender was not significantly associated with reporting blood in urine and/or reported blood in stool ($p>0.1$). After accounting for age, accessing unimproved water for any activity (including crossing) resulted in higher odds of reporting blood in urine and/or blood in stool (OR: 1.90; 95% CI: 1.07-3.36). About one out of seven (n=66, 13.5%) of the study participants reported to have taken anthelmintic drugs within the 6 months before the interview.

8.4.6 Knowledge of schistosomiasis and fascioliasis

Knowledge of schistosomiasis was very low among the study participants with only 22.9% reporting to ever have heard about schistosomiasis and merely 4.1% who could name details of the lifecycle of this parasite. Knowledge about fascioliasis was, despite its importance for livestock in the area, known to only 6.1% of the study population, while only 0.8% could recall details of the lifecycle. Individuals aged 8-15 years were the group least aware of these two diseases.

During the observation and the conversational interview we could see that urination in and around the water sources is quite frequent, especially at man-made dams (not so much at small water bodies). For defecation, people reported to go someplace next to the border of the water source. Animal manure could likewise be seen around the water source.

8.4.7 Rice cultivation

Of all participants reporting to work on a field, 80% (n=264) reported to be involved in rice cultivation. About half (52%) of those practicing rice cultivation used traditional fertilizer that consists of dried cattle dung and could thus contain *Fasciola* eggs. However, rice fields in the area can be both dry and wet cultures and the exact type of culture used by our study population is unknown. In total, 74% (n=83) of participants who reported blood in urine and/or blood in stool also reported practicing rice cultivation. Of all rice farmers who use traditional fertilizer, 31% reported blood in urine and/or blood in stool.

8.4.8 Consumption of raw vegetables, salad or untreated water

Treatment of drinking water in general was reported by 20.7% (n=101) of the study participants, whereas treatment of drinking water from unprotected sources was reported by 2.8% (n=4) of all participants that also reported drinking unimproved water (n=143). The consumption of salad and raw vegetables was reported by 80.0% (n=391), and 69.5% (n=340) of participants, respectively. When asked where these vegetables and salads were obtained, 42.3% (n=207) stated that they consume vegetables grown in their own gardens or fields, and 73.4% (n=359) stated that they consume vegetables purchased from the market. Vegetables and salads in the gardens and fields were watered mostly with unimproved water.

8.4.9 Presence of ruminants

About one-third of the study participants (n=147; 30.1%) reported to have seen ruminants in close proximity to open water sources during the 2 weeks prior to the

interview. Additionally, tracks of ruminants could be observed at 78% (n=28) of all unprotected water sources visited by the study team. During the 2 weeks prior to the interview, 89.1% (n=294) of study participants working in a garden had seen ruminants in close proximity to their agricultural plots.

8.5 Discussion

Although all participants in the current study conducted in the district des Savanes of northern Côte d'Ivoire had access to, and used, improved water sources, especially for consumption, this did not prevent them from contacting unimproved water sources. Indeed, the majority of people used unimproved water for certain activities with about one third even consuming unsafe water. Employing a mixed methods approach, consisting of direct observation and conversational interviews, we were able to understand that this was due to the fact that work places (most importantly agricultural fields) were often rather far away from any safe water supply. This forces people to enter into contact with potentially infectious water in a setting where *Schistosoma* transmission plays a role (Chammartin et al., 2014). Due to the many water bodies and the occurrence of suitable intermediate host snail species in the area, the population of the district des Savanes is considered to be at-risk of schistosomiasis (Hürlimann et al., 2011; Schur et al., 2013). Nevertheless, participants reported poor knowledge of schistosomiasis. This is in line with (Acka et al., 2010) who showed that particularly people who have never been exposed to research have less knowledge of schistosomiasis. Health education focusing on knowledge about schistosomiasis and its transmission along with protective measures and hygiene education could decrease risky behaviour pertaining to water contact. Yet, during our conversations with a teacher, we learned that the topic of schistosomiasis had been taken out of the curriculum only a few years ago. This teacher expressed surprise about our interest in schistosomiasis, as she had been under the impression that the subject was taken from the curriculum because the disease had been eliminated in Côte d'Ivoire. Furthermore, those participants who did know that schistosomiasis was still endemic in the country were surprised about

our specific interest in this disease. Schistosomiasis was widely perceived as a child's disease that would self-regulate once a person has grown up. The disease itself is seen as harmless and other diseases as well as everyday problems have much higher priority according to the study participants. Additionally, even with an established safe water supply, people would still need to get into contact with open water bodies for certain activities for which the use of improved water is not feasible or convenient. These factors have to be considered by projects that aim at reducing people's use of unsafe water. Programmes will have to think about how to ensure access to safe water, particularly when people spend a considerable amount of time in remote areas away from the villages, including agricultural activities. One possibility, at least concerning the consumption, would be the installation of protected wells and pumps closer to the fields.

People often have to cross open water by entering into the water in order to get to their various destinations even if they otherwise use exclusively improved water for daily activities. In view of the growing interest to eliminate schistosomiasis transmission (WHO, 2012b; Rollinson et al., 2013a) reducing risky water contact becomes of importance. In such an elimination setting, it would be increasingly relevant to also take the less obvious and less common transmission points into consideration. There is growing awareness that mass drug administration alone is insufficient to interrupt transmission and that rather a combination with education and the improvement of the sanitary situation has to be considered (Utzinger et al., 2003; Singer and de Castro, 2007; Singer, 2008; Gurarie and Seto, 2009; Utzinger et al., 2009b; Rollinson et al., 2013a). We also need to think about hygiene and sanitation at the place of work where many people are spending large amounts of their day. Defecation and urination is often performed in close proximity to water sources which can further spread infections. It might be worthwhile to also think about improving the sanitary condition near the water bodies either through education and social marketing or through the provision of sanitary structures close by (Knopp et al., 2012).

The presence of ruminants near unimproved water sources, as well as the habit of consuming untreated water from shared water sources, and eating raw

vegetables irrigated with the same water poses a potential risk for human infection with *Fasciola* spp. (Mas-Coma et al., 1999b). Prior studies found a high prevalence of *Fasciola gigantica* among ruminants in the northern part of Côte d'Ivoire (Achi et al., 2003d) that could transmit the disease to humans. Just as with humans, animal defecation takes place not far from the bank of the water source and *Fasciola* eggs can enter the water body once there is rain or other means that displaces the eggs into the water. The close interlinking of humans and animals with the ecology thus plays an important part in the potential risk for transmission of fascioliasis. Indeed, the same water is used for multiple purposes: to water animals, to be used by humans for occupational or recreational activities and for irrigation of vegetables and salad. Additionally, we observed that the fruits of water lilies growing in man-made lakes are consumed by local residents. The fruit has to be picked out of the water and the inside of the fruit is then eaten on the spot without further cleaning. This does not only lead people to get into open water where they can possibly become infected by schistosomiasis but also harbours the potential to consume encysted *Fasciola* metacercaria that might be on the outside of the fruit.

During this study we mainly focused on the potential for infection with *Schistosoma* and *Fasciola*. However, it is evident that the consumption of unsafe water as well as the direct contact with open water sources increases the risk for other diseases, such as diarrhoea. While risk-reduction for diarrhoeal diseases is very much possible through the provision of safe water supply, the same does not hold true for the exposure to schistosomiasis and fascioliasis, since people cannot limit their water contact to the safe environment of their home. People might be obliged to access, use and even consume unsafe water at their workplaces which are often agricultural fields far away from the next human dwelling and thus far away from improved water supply.

Over the course of this study we only investigated the sedentary village population. However, semi-nomadic Peulhs, who often live in small camps in close proximity to the villages studied here, have different water contact patterns and habits compared to the village population. Therefore Peulh settlements must be likewise considered during intervention programmes since they play an important

part in the overall human-animal-ecology system, and thus the epidemiology of diseases. Our study contributes to the better understanding of how water is being used by the population of northern Côte d'Ivoire and helps to assemble the whole picture of water contact and pertaining disease risks.

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9. Distribution of intermediate host snails of schistosomiasis and fascioliasis in relation to environmental factors during the dry season in the Tchologo region, Côte d'Ivoire

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9.1 Abstract

Background: Snail-borne trematodiasis, such as fascioliasis and schistosomiasis, belong to the neglected tropical diseases; yet, millions of people and livestock are affected. The spatial and temporal distribution of intermediate host snails plays an important role in the epidemiology and control of trematodiasis. Snail distribution is influenced by numerous environmental and anthropomorphic factors. The aim of this study was to assess the distribution and constitution of the snail fauna during the dry season in constructed and natural water bodies in the Tchologo region, northern Côte d'Ivoire, and to relate these findings to environmental factors and human infections.

Methods: Snails were collected using standard procedures and environmental parameters were assessed from a total of 50 water bodies in and around 30 randomly selected villages. A canonical correspondence analysis was performed to establish the relationship between snail occurrence and environmental factors. Furthermore, a total of 743 people from the same 30 villages and nearby settlements were invited for stool and urine examination for the diagnosis of *Fasciola* spp., *Schistosoma haematobium* and *Schistosoma mansoni*.

Results: Snails of medical importance of the genera *Biomphalaria*, *Bulinus*, *Lymnaea* and *Physa* were found. Differences in snail occurrence from sites sampled in December 2014 and snails sampled in February 2015, as well as between the northern and southern part of the study area, were revealed. Various environmental factors, such as temperature and human activities, were related to the occurrence of intermediate host snail species in the region. Only 2.3% of human participants tested positive for schistosomiasis, while no *Fasciola* eggs were found in stool samples.

Conclusion: We conclude that intermediate host snails of *Fasciola* and *Schistosoma* co-occur in water bodies in the Tchologo region and that the distribution of these snails correlates not only with environmental factors, but also with the presence of humans and animals and the environmental contamination of their excreta.

Keywords: Côte d'Ivoire, Fascioliasis, Intermediate host snail, Schistosomiasis, spatial distribution

9.2 Introduction

Fascioliasis and schistosomiasis belong to the neglected tropical diseases (Mas-Coma et al., 2009; Utzinger et al., 2011; 2012). Both diseases share similarities in their life cycles, of which the most prominent feature is the infection of specific aquatic snails that act as intermediate hosts (Nithiuthai et al., 2004). The distribution of intermediate host snails and abiotic environmental factors play an important role in the occurrence of infections (Appleton, 1978; Fuentes et al., 2005; Stensgaard et al. 2013). Indeed, the prevalence of suitable intermediate host snails is a determinant of infection risk (Mas-Coma et al., 2009; Adema et al., 2012).

It has been estimated that more than 250 million people are infected with *Schistosoma* spp (Keiser and Utzinger, 2009; Colley et al., 2014; Hotez et al., 2014a) and an estimated 2.6 million people are infected with *Fasciola* spp. (Grimes et al., 2015). Fascioliasis has considerable veterinary and economic consequences, while human infections with this liver fluke has long been considered a secondary zoonotic disease (Mas Coma et al., 1999). However, human infections are on the rise and it is estimated that 27.7 million people are at risk of acquiring fascioliasis (Esteban et al., 1998; Mas-Coma et al., 1999a; Keiser and Utzinger, 2005b; Mas-Coma et al., 2009 a, b).

Intermediate hosts for fascioliasis and schistosomiasis are aquatic snails of the families *Lymnaeidae* and *Planorbidae* (Mas-Coma et al., 2009a; Nithiuthai et al., 2004). A variety of abiotic and biotic factors, as well as human and animal presence, are known to be interrelated with the occurrence and spread of suitable intermediate host snails for fascioliasis and schistosomiasis (Appleton, 1978; Huang and Manderson, 1992; Fuentes et al., 2005; Stensgaard et al. 2013; Afshan et al., 2014). Some work has been performed concerning snail distribution in different parts of Côte d'Ivoire (Njiokou et al., 1994; Utzinger et al., 2000; Raso et al., 2005; Yapi et al., 2005; Coulibaly et al., 2012; Assaré et al., 2014). Importantly though, the majority of research has focused on western and south-central Côte d'Ivoire,

because these are, historically, the best known foci of human schistosomiasis. It should also be noted that a decade-long political crisis has rendered research in the northern part of Côte d'Ivoire exceedingly difficult (Bonfoh et al., 2011; Bony et al., 2013; Koné et al., 2013). The study reported here is part of a larger project pertaining to the systems epidemiology of schistosomiasis and fascioliasis in the northern part of Côte d'Ivoire, which investigates a variety of factors ranging from socio-cultural to ecological and methodological considerations in the fight against these two diseases. The aim of the present work was to assess the composition and distribution of the snail fauna in water bodies in the Tchologo region of the District des Savanes in northern Côte d'Ivoire, and to interrelate these findings with environmental factors as well as the occurrence of human schistosomiasis and fascioliasis.

9.3 Materials and Methods

9.3.1 Ethics statement

The study protocol has been approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland). Ethical approval has been granted by the ethics committees of Basel (reference no. EKBB 64/13) and Côte d'Ivoire (reference no. 32-MSLS/CNERdkn). District health and village authorities were informed about the purpose and procedures of the snail surveys and granted their approval. Study participants and parents/guardians of individuals aged <18 years were informed about the purpose and procedures of the study, including potential risks and benefits. Written informed consent was obtained from participants or parents/guardians of minors before the start of the interviews. Participation was voluntary, and hence, people could withdraw from the study at any time without further obligation. All results were coded and treated confidentially.

9.3.2 Study area, water sites and population

The northern part of Côte d'Ivoire is characterised by a West Sudanian savannah climate with a distinct rainy season from June to October. The mean annual

precipitation ranges between 600 mm and 1,000 mm. The dry season lasts from November to May and is marked by the Harmattan, a hot and dry wind from the Sahara that occurs between December and February. This Harmattan period is marked by cold nights, hot days and low humidity and is followed by an upsurge in temperature from the end of February to mid-March.

The ecology is characterised by grass- and woodlands on red and grey clay soils (ultisol and alfisol), interspersed by many small rivers (draining from North to South), small water bodies that often drain during the dry season and small water reservoirs (dams) which have been constructed, starting in the 1970s, to promote and further develop livestock farming and irrigated agriculture (Aka et al., 2000; Fund, 2014). Many of these small lakes were stocked with fish to establish aquaculture. The region of Tchologo, with its capital Ferkessédougou, is part of the district des Savanes in the North of Côte d'Ivoire. It is situated between 8.6153° and 10.4655° N latitude and 3.8067° and 5.9845° W longitude, with a total surface of 17,728 km². To the North and North-East, it shares borders with Mali and Burkina Faso, respectively (Figure 8.1). The predicted prevalence of human schistosomiasis in the area is very low (<1%) (Chammartin et al., 2014). This has been confirmed by recent surveys, though some villages were identified with prevalence of *S. haematobium* among school-aged children of about 10% (Eliézer K. N'Goran and colleagues, unpublished data). Based on these findings, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) has launched a new study to investigate whether schistosomiasis can be eliminated in this part of Côte d'Ivoire by an integrated control approach (preventive chemotherapy plus snail control). Previous studies reported *Fasciola* prevalence in animals of 10-20%, depending on the livestock species (Achi et al., 2003 a, b). Hence, the area is co-endemic for schistosomiasis and fascioliasis and the presence of specific intermediate host snails is suspected.

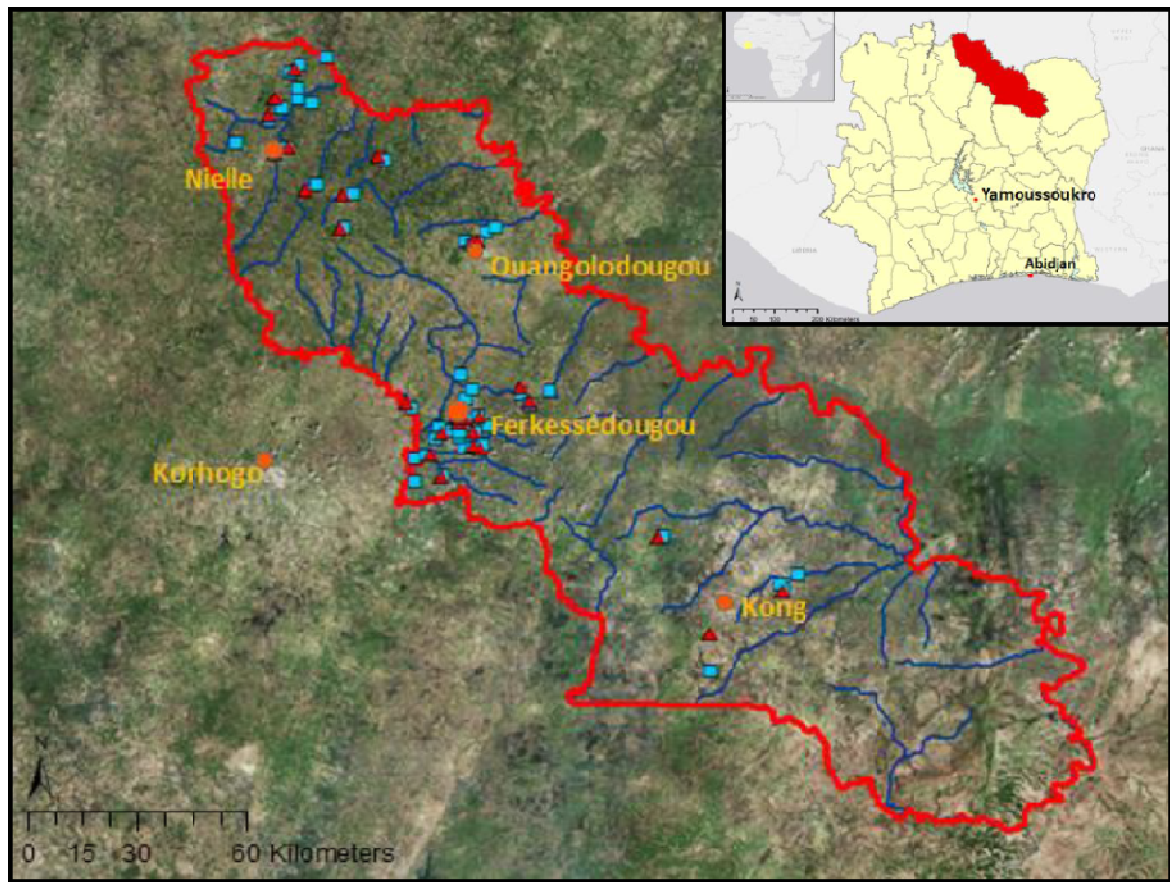


Figure 9.1 Map of the study area: Main map showing the region of Tchologo (red borders) with its rivers (blue lines). Blue rectangles represent the water sites visited and red triangles the 30 villages chosen. Orange dots depict the towns named on the map. The small map on the right (top) localises the Tchologo area within Côte d'Ivoire and Africa

9.3.3 Malacological survey

Snail sampling was pursued by a trained field worker. Following standard procedures (Ouma et al, 1989), snails were collected over a single 15-min period at each site to a distance of up to 1.5 m off shore using a long-handed kitchen scoop (1.5 m pole; 2 mm mesh size). Sampling sites were carefully selected by local guides after discussion with village key informants. The key selection criterion was that human-water contact occurred at the site. Snail collection was done at the shore of the water body where humans contact the water. Snails were measured and identified to the genus level using an identification guide adapted from the

morphological key put forth by Mandel-Barth (1962). Each sampling location was geo-referenced using a hand-held tablet computer (Samsung Galaxy Tablet 2 and Samsung Galaxy Tablet 3). Shedding experiments were attempted but external factors such as extreme heat and long transport ways for the snails rendered them unfeasible and ultimately unsuccessful.

9.3.4 Habitat data

Water parameters and biological characteristics were determined and human-water activities recorded and directly entered into an electronic survey form using open data kit (ODK by Borriello et al., 2008). Water temperature (°C), conductivity ($\mu\text{S}/\text{cm}$), salinity (ppt), total dissolved solids (mg/l), pH and redox potential (mV) were measured using a portable multimeter (Hach-Lange®, HQ30D; Düsseldorf, Germany). Water samples were taken at a distance of 0.5-1.0 m from the shore, in close proximity to where snail sampling occurred.

Type and quantity of aquatic vegetation within sight of the snail-sampling point (emergent, floating, subaquatic and detritus) were registered. The presence of animals was recorded through direct observations (actual presence of animals) and by recording footprints of cattle, goats, sheep or other animals. Type and extent of pollution at the sampling sites were noted. It was distinguished between solid and liquid pollution and particular emphasis was placed on human and ruminant excreta. Water contact activities were assessed through direct observations and interviews with the person guarding the dam or other local people. The choice of parameters and their classification was loosely guided by Abdel Malek (1958), Appleton (1978), Madsen (1987), Utzinger et al. (1997a, 1997b), Matthys et al. (2006), Bony-Kotchi et al. (2013), Koné et al. (2013) and Musard (2014).

9.3.5 Parasitological examinations

Clinical specimens for determining *Schistosoma* infection consisted of single urine and stool samples obtained from 743 individuals in 30 villages. Urine samples were subjected to a standard urine filtration method (10 ml of urine) for detection of

S. haematobium eggs and reagent strips (Hemastix®, Bayer Diagnostics; Basingstoke, United Kingdom) for microhaematuria (Krauth et al., 2015a). Stool samples were subjected to the Kato-Katz thick smear method for detection and quantification of *S. mansoni* eggs (Katz et al., 1972).

9.3.6 Statistical analysis

Canonical correspondence analysis

To illustrate the relationship between the different snail species and selected environmental variables, a CCA was conducted (Ter Braak, 1986; Legendre & Legendre 2012). The CCA was restricted to those sites where complete data records were available and where at least one snail species was present (n=27). Ten of the 26 environmental variables were found to be important and were included in the CCA. The excluded variables were found to either have little explanatory power or to correlate strongly with one another.

The CCA was performed in the statistical environment R, version 3.0.2 (R Foundation for Statistical Computing; Vienna, Austria), using the package 'vegan'. Scaling type 2 (i.e. species scaling) was employed to emphasise the relationship among species.

Of note, the CCA is an ordination method with the goal to project the multidimensional relationship in a 2-dimensional graph. With canonical correlation, several dependent variables are correlated simultaneously. For each set of variables, linear combinations are established in an attempt to identify the maximum simple correlation between the sets of dependent and independent variables. The CCA provides information on the overall correlation of dependent variables, as well as between each of the independent variables.

In the interpretation of our results on snail occurrence, the following considerations need to be kept in mind: In the CCA, we correlate the abundance of several snail species with several environmental factors. However, since a given water site is a finite space with limited resources, the presence of snails from one species will also have an influence on the presence of others. Moreover, the preferences for certain environmental parameters are unimodal, situated between a

lower and an upper limit, which are both equally unfavourable. It is, in the end, the combination of different environmental factors (including factors not measured) that make a habitat favourable for intermediate host snails. Hence, the predicted optima for single parameters for the snail presence should be seen in relation to other parameters in the same water site (Hait et al., 2006).

9.4 Results

9.4.1 Distribution of intermediate host snails in the Tchologo region

In A total of 50 human-water contact sites in close proximity to the main settlements of the 30 study villages were sampled for snails once either in December 2014 or in February 2015. In January 2015 no sampling took place. Complete data records were available for 49 sites, including snail collection, habitat characterisations and physico-chemical parameters. Snails were found in 29 sites with 28 harbouring snails that might act as intermediate hosts for *Schistosoma* and/or *Fasciola*. Of the 230 collected snails, 119 (from 24 sites) belonged to *Schistosoma* intermediate host species from the genera *Biomphalaria* and *Bulinus*, 75 (from 13 sites) belonged to *Fasciola* intermediate host species from the genera *Physa* and *Lymnea*. The remaining 36 snails (from four sites) were of no medical importance (Figure 8.2).

Of the 19 sites in the North, 14 (74%) harboured snails, whereas 13 out of the 26 sites in the centre (50%) and two out of five sites in the South (40%) harboured snails (Figure 8.3). Differences in the spatial and temporal occurrence of intermediate host snails were observed. While *Biomphalaria pfeifferi* was found throughout both sampling periods (December 2014 and February 2015) and throughout the region, the majority of *Biomphalaria* snails (84%) were collected in in just 10 villages in the December 2014 survey. *Lymnea natalensis* was more frequently found in February 2015 (9/18 villages) compared to December 2014 (1/11 villages) and were more abundant in the North, where 92% of all *Lymnea* snails were found. Most *Bulinus* snails were found in February 2015. *Bulinus globosus* was exclusively found in February 2015 (in 11 out of 18 villages; Figure 8.4). Both

schistosomiasis and fascioliasis intermediate host snails were present at all altitudes with a peak abundance around 340 m above sea level.

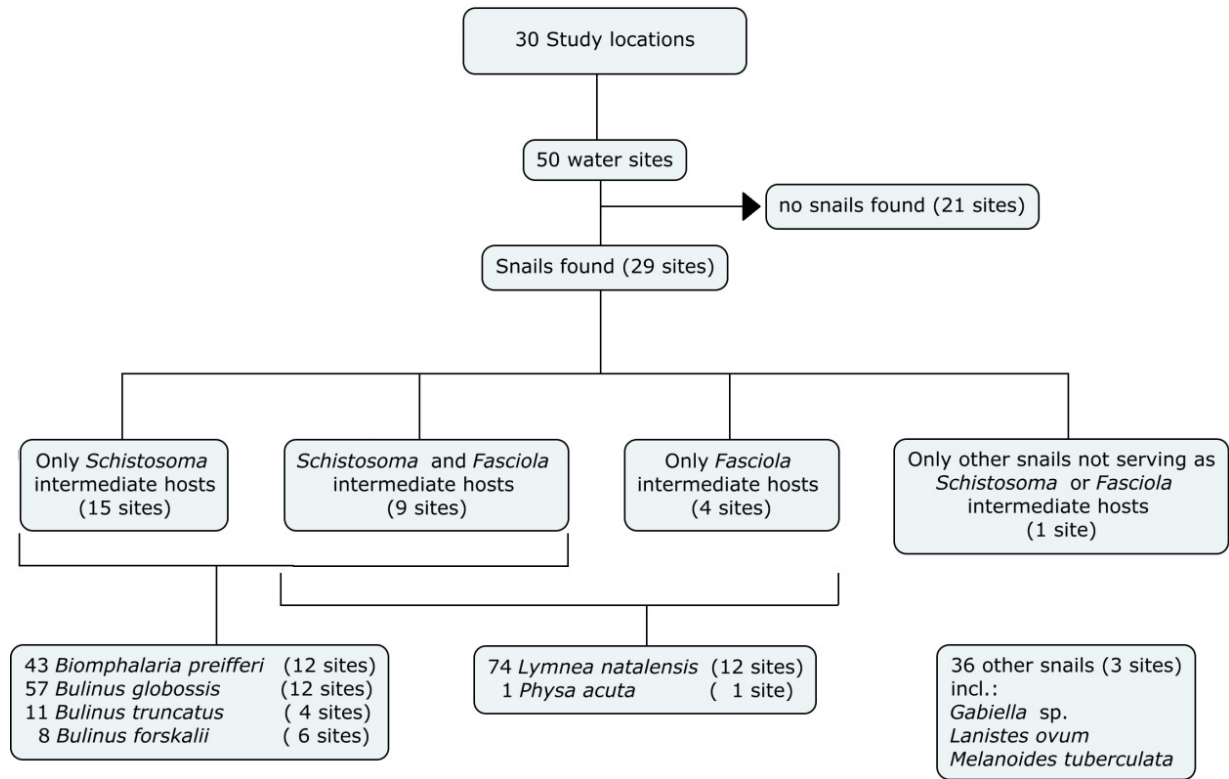


Figure 9.2 Flow chart of sampled water bodies and snail species from the Tchologo region, northern Côte d'Ivoire Dec. 2014 and Feb. 2015

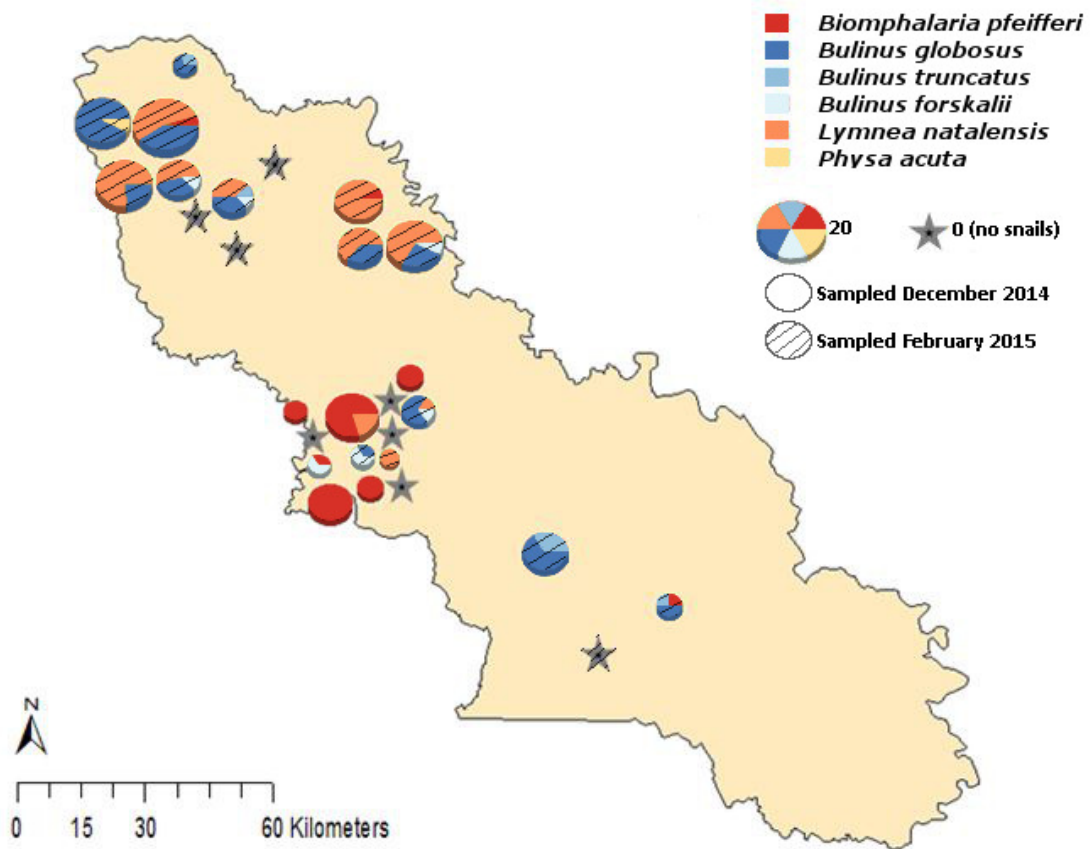


Figure 9.3 Snail distribution at studied water sites in the Tchologo region, northern Côte d'Ivoire Dec. 2014 and Feb. 2015

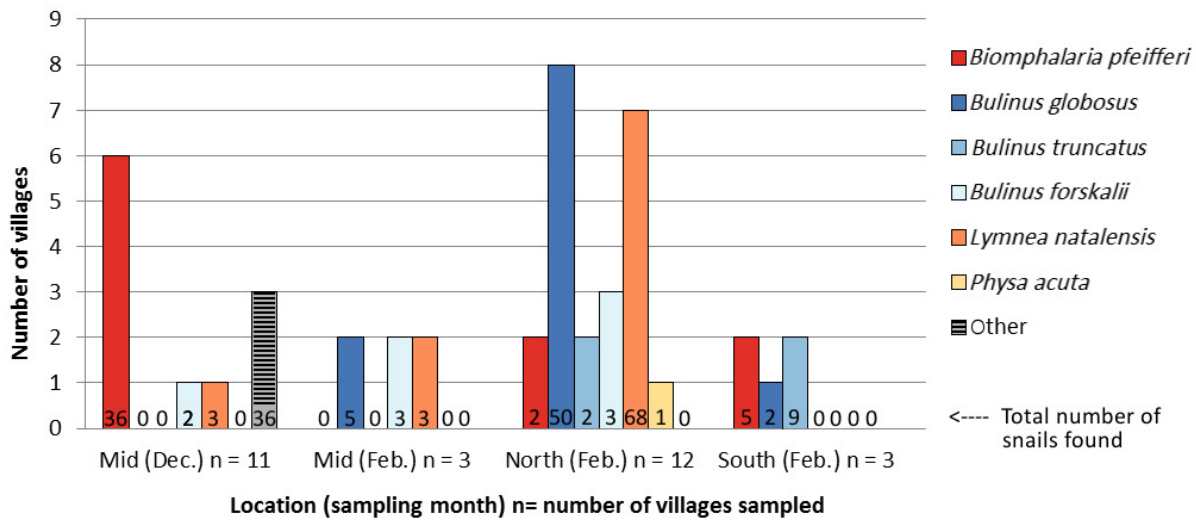


Figure 9.4 Collected snail species by sampling time and location. Note: 1 to 4 water bodies were investigated per village

9.4.2 Habitat characteristics and determinants of snail presence

Snails were found predominantly in man-made dams and small stagnant water bodies (local name: marigots). Indeed, 21 of the man-made dams (70%) harboured snails, whereas in four marigots (33%) and three river sites (37%) snails were found. The snail fauna, stratified by type of water body, is illustrated in figure 8.5. *Biomphalaria* snails were found in all types of water bodies where any snails were found. *Bulinus globosus* and *Bulinus truncatus* were almost exclusively found in man-made dams. *Bulinus forskalii* were also collected from rivers (22% of all *Bulinus forskalii*) (Figure 8.6).

Table 8.1 presents an overview of the range of temperature, pH values, conductivity and redox potential for the entire area, in sites harbouring *Schistosoma* intermediate host snails and in water bodies harbouring *Fasciola* intermediate host snails. Water temperature in the entire study area ranged from 21.5°C to 34.4°C across all sampling times. The mean water temperature of 28.9°C (standard deviation (SD) 3.2°C) is slightly lower than at sites with *Schistosoma* intermediate host snails (29.6°C, SD 3.6°C).

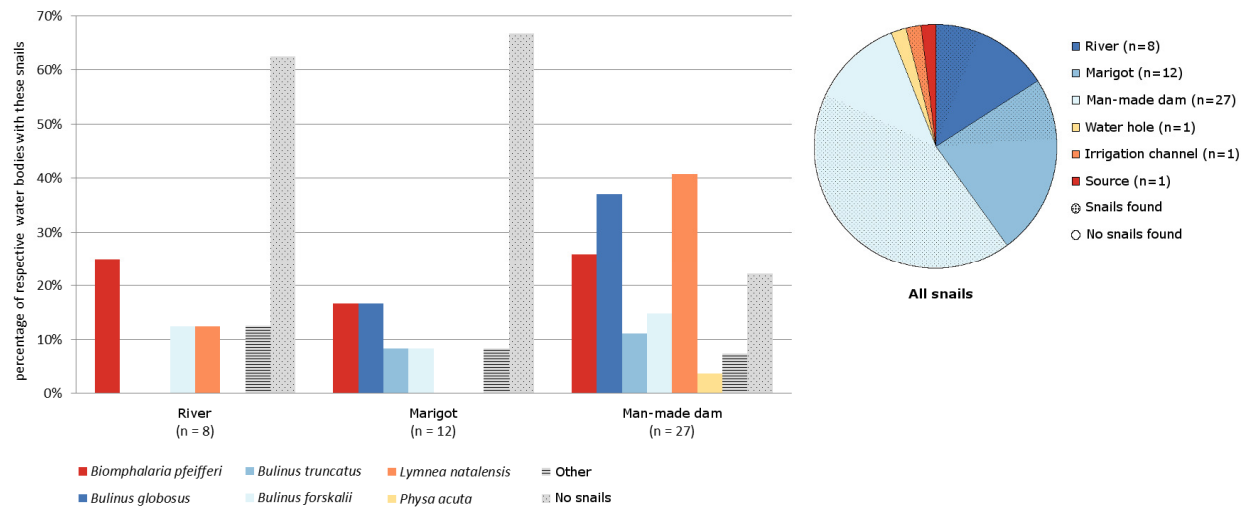


Figure 9.5 Snail fauna in different types of water bodies

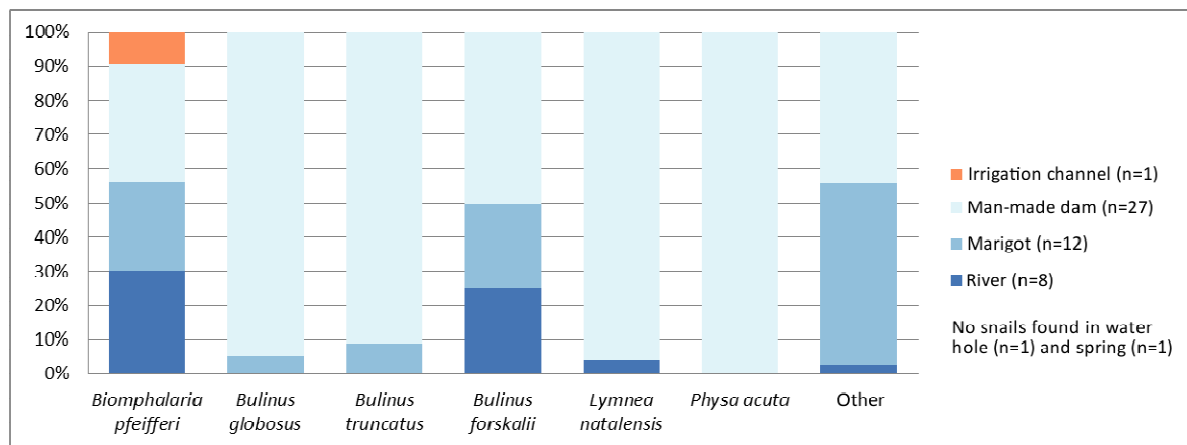


Figure 9.6 Snail findings stratified by water types

9.4.3 *Schistosoma* infections in humans

The prevalence of schistosomiasis in the study area was very low; 2.2% of the participants tested positive for *S. haematobium* with urine filtration and 1.0% tested positive for *S. mansoni* with the Kato-Katz technique or a more sensitive point-of-care circulating cathodic antigen urine cassette test. Microhaematuria, a widely used proxy for *S. haematobium* infection (Ochodo et al., 2015), was present in 13% of study participants (Krauth et al., 2015a). Slightly more microhaematuria was present

in the central and southern areas compared to the North of the Tchologo region, whereas laboratory confirmed cases of urogenital schistosomiasis were found mostly in the North (Figure 8.7).

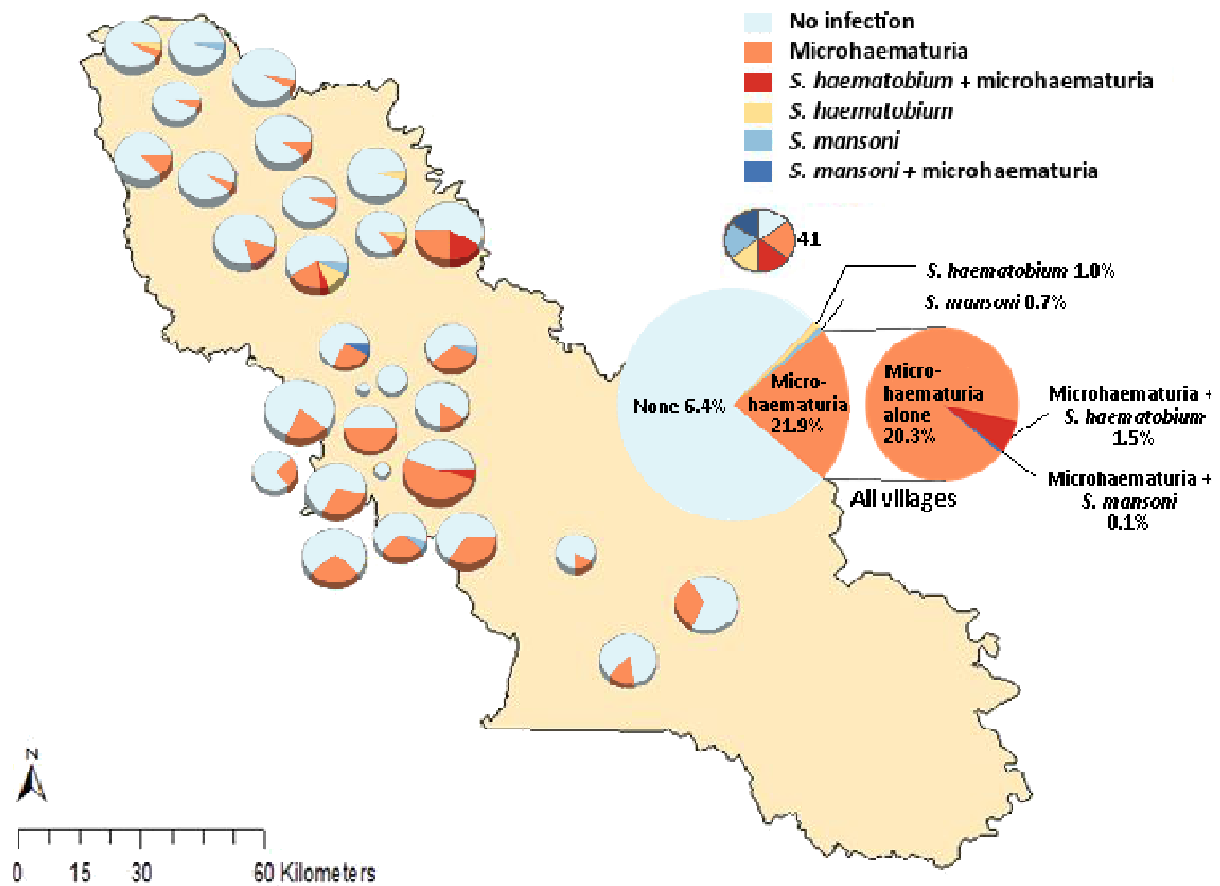


Figure 9.7 Prevalence of participants tested positive for *S. mansoni*, *S. haematobium*, microhaematuria, or combinations of the former in 30 study villages in the Tchologo region, northern Côte d'Ivoire Dec. 2014 and Feb. 2015. *S. haematobium* was tested with urine filtration, *S. mansoni* was tested with Kato-Katz thick smear and microhaematuria was tested with reagent strips.

Table 9.1 Physico-chemical water parameters of water sites in the Tchologo region, northern Côte d'Ivoire

	Temperature (°C)			pH			Conductivity (µS/cm)			Redox potential (mV)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Entire area	28.9	3.2	21.5-34.4	6.9	0.6	5.5-8.9	107.8	62.4	34-340	107.7	66.3	-104.6-350.6
SIHS	29.6	3.6	22.2-34.5	7.0	0.4	6.5-7.7	126.0	85.2	49-340	191.3	48.6	132.1-350.6
FIHS	30.5	1.1	26.2-33.7	7.3	0.8	6.7-8.9	102.1	50.1	34-152.2	166.7	18.0	123.6-242.7

SIHS, *Schistosoma* intermediate host snails; FIHS, *Fasciola* intermediate host snails.

9.4.4 Results from the CCA

Selected variables found to be relevant for the CCA were pH, temperature, conductivity, and the binary variables river, marigot, substrate, turbidity, subaquatic vegetation, surface vegetation (i.e. emergent vegetation) and detritus. Figure 8.8 shows the main pattern of variation in community composition explained by the environmental variables and depicts the distribution of the three snail genera *Bulinus*, *Biomphalaria* and *Lymnaea* in connection with these variables.

Lymnaea snails

The presence of *Lymnaea* snails was positively associated with subaquatic vegetation, pH and temperature. Ideal habitats for *Lymnaea* in our sample had a temperature of 30.8°C, a pH value of 7.3 (SD 0.8) and a higher than average amount of subaquatic vegetation (>20% of the visible, underwater area covered in vegetation). Furthermore, there was a tendency to find *Lymnaea* at sites with less detritus (i.e. particles of any material, including organic material, live parts of leaves, etc. with a size visible by the eye and larger than a grain of sand), a more small-grained substrate (i.e. sand and mud ground) and less turbid waters (only little amount of floating particles through which the ground or at least the deeper levels of the water can be seen). Furthermore, *Lymnaea* snails were less frequently found in ponds and rivers than the other two snail genera.

Biomphalaria snails

Biomphalaria snails were often found in rivers and ponds and they predominantly inhabited sites that were turbid (moderate to high amount of floating organic particles such as parts of leaves or grass through which the ground cannot be seen) and have a coarser substrate than most other sites (coarser than mud or sand, with visible particles of organic materials, pebbles or stones). Habitats were characterised by a lower temperature (27.8°C) and a lower pH value (6.8, SD 0.6) than the average measured in all sites. Except for emergent vegetation, *Biomphalaria* snails were not associated as strongly with water vegetation as

species from the other two genera. Sites where *Biomphalaria* snails were found were characterised by little emergent vegetation.

Bulinus snails

The presence of *Bulinus* snails strongly correlated with conductivity and detritus. *Bulinus* snails showed preferences for sites with relatively higher conductivity (around 127 $\mu\text{S}/\text{cm}$) when compared to *Lymnaea* (114 $\mu\text{S}/\text{cm}$) and *Biomphalaria* (89 $\mu\text{S}/\text{cm}$). Regarding temperature (29.8°C), pH (7.1) and turbidity, typical characteristics of *Bulinus* habitats were in between those of *Lymnaea* and *Biomphalaria* and corresponded to an average water site in the region. While *Bulinus* snails were found in ponds, they were absent from rivers. Furthermore, habitats of *Bulinus* were characterised by slightly coarse substrate and a decent amount of emergent vegetation, but less subaquatic vegetation compared to habitats where *Biomphalaria* and *Lymnaea* were present. Although distinct from the others genera, ideal *Bulinus* habitats are situated in between the habitats of *Biomphalaria* and *Lymnaea* regarding most environmental factors investigated.

Optima of *Biomphalaria* and *Lymnaea* habitats are oppositional in many environmental factors. Although distinct from the others species, ideal *Bulinus* habitats are situated in between the habitats of *Biomphalaria* and *Lymnaea* regarding most environmental factors. Moreover, *Bulinus*' preferred habitats are relatively similar to an average water site in the study area.

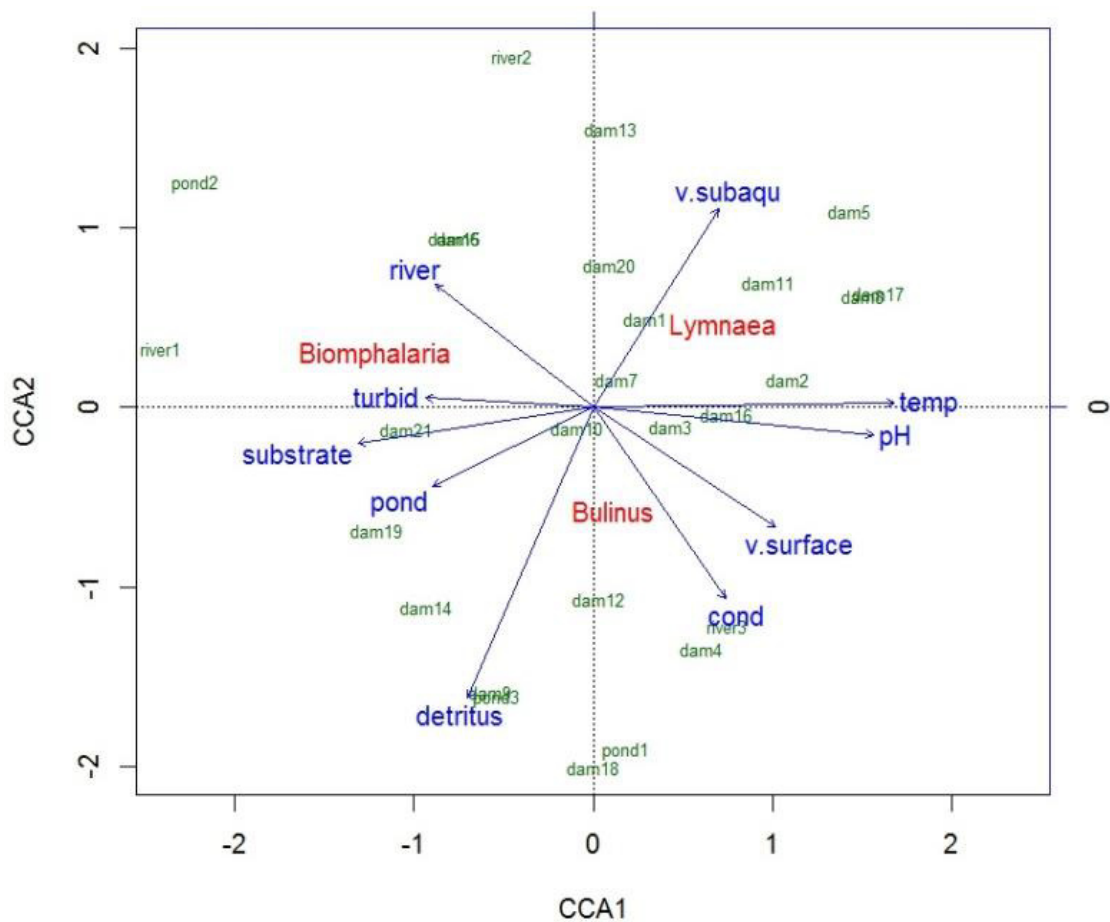


Figure 9.8 Canonical correspondence analysis ordination triplot

The diagram (scaling type 2) displays the abundance and distributional similarity of 3 snail genus (red) at 27 sampling sites (green) in Tchologo related to environmental variables (blue arrows). The axes CCA1 and CCA2 represent the linear combinations of the environmental variables.

9.4.5 General features

In general, sites with *Fasciola* intermediate host snails had higher water temperatures and mean pH values than sites with *Schistosoma* intermediate host snails, but lower conductivity values and redox potentials. *Fasciola* intermediate host snails were more often present in habitats with higher temperature and had a smaller tolerance range than *Schistosoma* intermediate host snails (Table 1). In habitats that were shared by both types of intermediate host snails, the median

temperature was closer to those of “*Schistosoma* intermediate host snails only” habitats. Water sites where no snails were found tended to have lower median temperatures than habitats where snails were found. Yet, the range of water temperatures for “no snails” habitats was quite large. Regarding the regional distribution, habitats in the centre tended to have the lowest temperature median, similar to that of habitats where no snails were found. Moreover, temperatures in the North tended to be higher than in the other regions and rather similar to habitats of *Fasciola* intermediate host snails or shared habitats. With respect to *Schistosoma* intermediate host snails, the probability of snail presence was highest when water temperatures were around 29-30°C. *Fasciola* intermediate host snails only showed the highest probability of presence at sites with temperatures at around 31-32°C.

9.4.6 Further factors not included in the CCA

Type and dimensions of water sites

Of all water sites that were shown to our research team by the local communities, 43% were natural water sites (including rivers, marigots and springs), while the remaining 57% were man-made water sites (dams, irrigation channels and water holes). Significantly more intermediate host snails for both fascioliasis and schistosomiasis were found in constructed compared to natural water bodies (75% vs. 29%). Especially intermediate host snails for fascioliasis were found predominantly in constructed water sites. Furthermore, in only 32% of all rivers and 25% of all marigots snails were found. Nevertheless, intermediate host snails for fascioliasis only occurred in water sites with at least some extent of flow, whereas intermediate host snails for schistosomiasis also occurred in stagnant water but to a lesser extent. Generally, significantly more intermediate host snails occurred at flowing water (>0.01 m/s) than stagnant water ($p<0.05$).

Presence of animals

Overall, animals and/or footprints thereof were present at 42 of the 50 sites investigated (84%). More snails were found in sites with animals in or around the site, namely at 59% of sites with animals and at 28% of sites without animals. Especially the presence of ruminants strongly correlated with snail presence. Overall, snails were present at 66% of sites with ruminants and at only 9% of sites without ruminants ($p < 0.05$).

Intermediate host snails of fascioliasis were exclusively found at sites where the presence of animals was recorded. In particular, such intermediate host snails were found at 38% of sites with ruminants and only at 4% of sites without ruminants. Intermediate host snails of schistosomiasis were likewise found at only 25% of sites without ruminants. Cattle in particular showed strong correlation with the presence of *Schistosoma* intermediate host snails with *Schistosoma* intermediate host snails being present at only 9% of sites without prints of cattle and at 40% of sites with cattle prints.

Pollution and excreta

Polluted water sites (a combination of solid and liquid wastes and excreta from humans and ruminants inside or around water bodies) were less frequently inhabited by snails (44%) than sites without such pollution (66%). However, at the few sites ($n=3$) with moderate pollution, the share of schistosomiasis intermediate host snail presence was higher than at site with no or little pollution. Similarly to sites with cattle footprints, the few water points with ruminant excreta (but little other pollution) showed a considerably higher rate of snail presence (68%) than sites without such excreta (9%). There was only one site where intermediate host snails for both fascioliasis and schistosomiasis were present, although no ruminant excreta were observed. Apart from this site, snails were exclusively found at sites polluted by ruminant excreta ($p < 0.001$). Regarding the presence of human excreta, we only found a small difference in snail distribution between sites with or without human excreta with intermediate host snails of fascioliasis being slightly less present at water sites with human excreta (16% at sites without human excreta vs. 25% at sites with human excreta).

Water use and human influence

In 61-69% of all water sites where activities brought humans into direct physical contact with water, intermediate host snails were found (51-69% were inhabited by intermediate host snails of schistosomiasis). In 50-100% of sites where water was directly (drinking or religious mouth washing) or indirectly (through irrigation or water plants) consumed, intermediate host snails were found, whilst in 12-50% of these, intermediate host snails of fascioliasis were present. In all sites where plants were being collected by humans, intermediate host snails were found (50% for fascioliasis and 72% for schistosomiasis). Snails only occurred at sites where animal husbandry was practiced (61%) and no snails were found in water bodies where no animal husbandry was done (Figure 8.9).

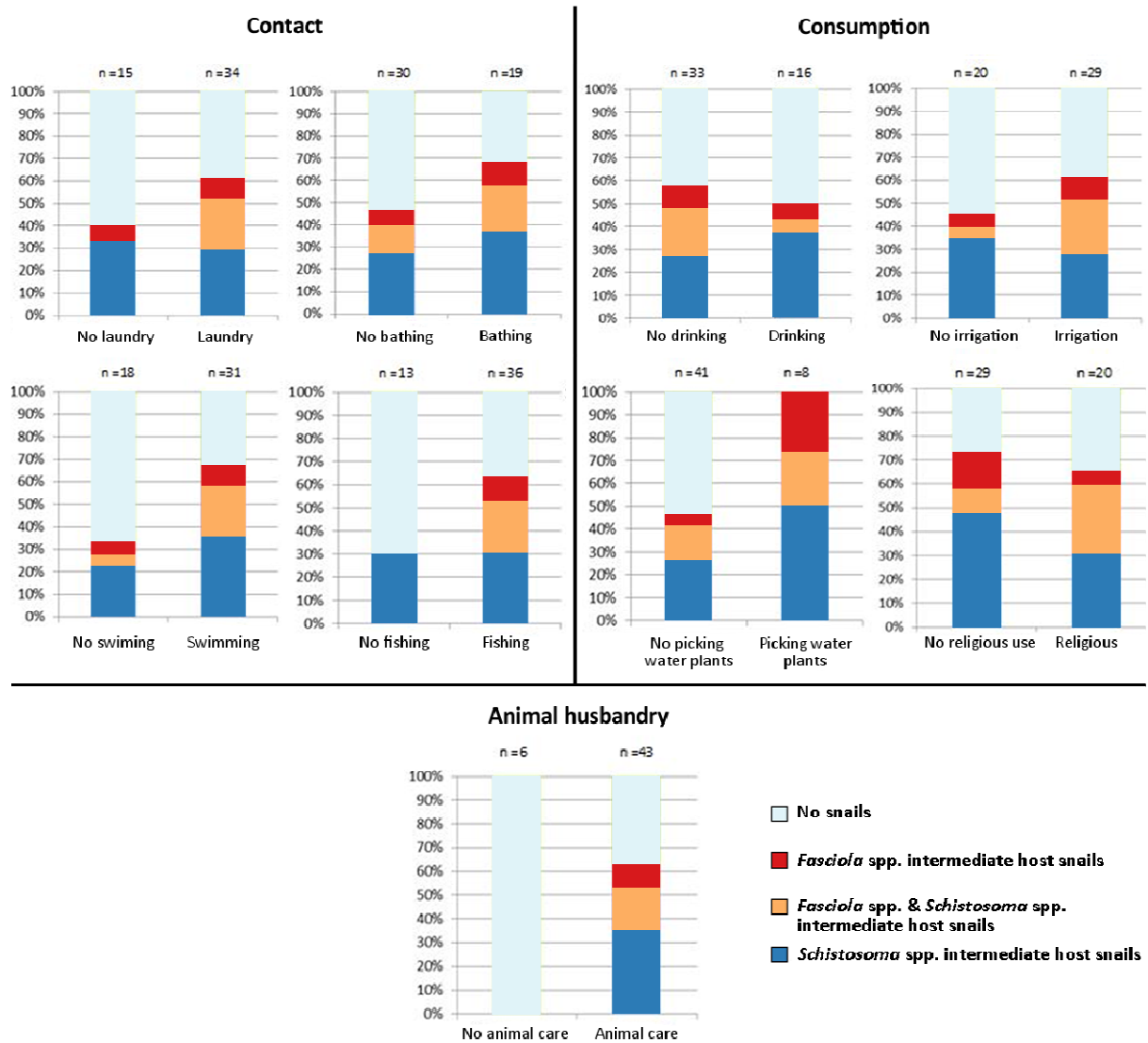


Figure 9.9 Snail presence in water points stratified by water-related activities

9.5 Discussion

This study was performed within the larger “systems epidemiology” project, which was implemented between August 2013 and July 2015 in northern Côte d'Ivoire (Krauth et al., 2015 a, b) and the Lake Chad area in Chad (Greter et al., 2015; 2016). The main objective of the systems epidemiology project is to deepen the understanding of *Schistosoma* and *Fasciola* infections in humans and livestock in relation to the social-ecological systems. The work presented here established the presence of intermediate host snails for *S. haematobium*, *S. mansoni* and *Fasciola* spp. in the Tchologo region in northern Côte d'Ivoire for the dry season of 2014/2015.

A note on the study season: Although some authors suggest, that snails are more abundantly found during the rainy seasons (Preston and Castelino, 1997) and transmission of schistosomiasis might therefore be more likely during the rainy season, many study participants reported to access open surface water more often during the dry season due to the desiccation of wells and other water resources. Human water contact is arguably a more important factor for disease transmission than the mere occurrence or even infection rate of intermediate snail hosts in the water body (Pennance et al., 2016). And although snails might be more abundant during the rainy season, previous research shows that *planorbidae* snails, to which the *Bulinus* and *Biomphalaria* genera belong, remain present in water points during the dry season and even remain infested with and keep shedding *Schistosoma* parasites (Brown, 1994; Moser et al., 2014; Senghor et al., 2015). Other authors even found that *B. globosus*, *B. pfeifferi*, and *L. Natalensis* showed a peak abundance during the hot, dry season, in their study area (Woolhouse and Chaniwana, 1998; Monde et al., 2016). This observation can also be attributed to a higher aggregatedness of snails during the dry season as opposed to the rainy season. Indeed, Woolhouse and Chaniwana (1988) found that patchyness and aggregatedness of snail populations were different depending on the season, with snails being more aggregated during the dry season and more patchily distributed during the rainy season (Woolhouse and Chaniwana, 1998). In combination with the

aforementioned seasonally dependent human behavior, it follows that the dry season is indeed a reasonable time to survey intermediate host snails for schistosomiasis and fascioliasis, notwithstanding the fact that the total snail population can be expected to be larger during the rainy season. Concerning potential molluscicidal intervention, a higher level of aggregatedness and a heightened survival stress for the snails during the dry season, would make the dry season an optimal entry point for snail control.

The sampling of water points was done in the 30 villages, previously selected for the current study. Water points were identified by asking key informants from the local population to indicate water bodies frequently accessed by the villagers. Our sample thus is clustered, reflecting the dense population around constructed roads and other infrastructure and less dense populations further away from these areas. It follows that less densely populated areas are underrepresented in the sample, which was expected for a study that is interested in the transmission of schistosomiasis and fascioliasis, which are governed by human water contact patterns (schistosomiasis) and consumption of water plants (fascioliasis) (Esteban et al., 1998; Nithiuthai et al., 2014; Grimes et al., 2015; Krauth et al., 2015a).

Schistosomiasis, especially urogenital schistosomiasis, is endemic in the human population in this area, albeit with a low prevalence of 2.2%, while *S. mansoni* showed a prevalence of only 1.0%. In view of such low prevalence rates in the human population, the area is of particular interest to demonstrate the proof-of-concept of whether a combined pharmaceutical intervention (mass deworming with praziquantel) with snail control (targeted application of niclosamide) allows to interrupt the transmission of *S. haematobium*, which is the declared objective of a new SCORE project in the northern and central part of Côte d'Ivoire. There is historic evidence that schistosomiasis elimination can be achieved and a large, multi-year contemporary study is being implemented on the islands of Zanzibar (Knopp et al., 2012; Rollinson et al., 2013).

Comparing the distribution of intermediate host snails of the genera *Biomphalaria* and *Bulinus* to the distribution of human schistosomiasis cases indicates that the predominant occurrence of *Bulinus* species in the North of the region might indeed

be a spatially distinct distribution pattern. Since schistosomiasis is a chronic disease unless treated, there is no seasonal fluctuation to be expected in the prevalence of human disease (Utzinger et al., 2011; Colley et al., 2014). Laboratory confirmed cases of *S. haematobium* were found in five out of 13 villages in the North and in only one of 16 villages in the centre and South. These patterns correlate with the occurrence of *Bulinus globosus* predominantly in the North (eight out of nine sites where snails were found vs. in the South, four out of eleven sites where snails were found). These observations suggest that the detection of *Bulinus* species predominantly in the North is at least partially a spatial effect rather than only a difference between the beginning and the end of the dry season. To answer the question about spatial and temporal distribution patterns of different intermediate host snails, longitudinal studies with repeated malacological surveys are needed.

The CCA showed that *Lymnaea* and *Biomphalaria* species have distinctively different optima for environmental factors, whereas environmental optima of the *Bulinus* genus was in between the optima for *Lymnaeidae* and *Biomphalaria* and closely resembled the average water body characteristics in the study area. Other groups reported differences in environmental factors between different snail species, but concluded that two main factors are the most important drivers of intermediate host snail presence: flow velocity and temperature, whereas other factors such as conductivity or pH often had only minor or negligible influence (Barbosa et al., 1994; Angelo et al., 2014; Dida et al., 2014). The importance of man-made water resources such as dams and irrigation systems that form suitable habitats for snails of medical importance (Dzik, 1983; Yapi et al., 2005; Steinmann et al., 2006; Afshan et al., 2014) was confirmed by our study. Interestingly, our observations suggest that constructed water sites harboured more snails than natural water bodies. The higher snail abundance at man-made water sites could be partly influenced by two underlying factors, namely slower flow velocities and higher rates of pollution with organic matter due to human and livestock activities. Lenient water bodies have repeatedly been found to greatly influence snail abundance (Madsen et al., 1992; Dida et al., 2014). Furthermore, it was suggested that the higher availability of organic substances due to human activities in such water points fosters snail

abundance (Madsen et al., 1992; Barbosa et al., 1994; Rosso et al., 2003; Dida et al., 2014). This observation is again strengthened by our finding that human and livestock activities around water sites also correlate with snail presence. In many water sites studied here, people entered into direct physical contact with the water and we found intermediate host snails of schistosomiasis during a snapshot of 15-min of snail sampling. At all sites where some aquatic plants were collected for consumption, *Fasciola* intermediate host snails were present. These findings show that there is a persisting risk for sustained transmission of fascioliasis and schistosomiasis in the Tchologo region of northern Côte d'Ivoire.

For the interpretation of our findings regarding environmental parameters, it has to be considered that we could only focus on measurable parameters at the time of the survey, without accounting for the possibility that these factors change over time (diurnal and seasonal patterns, such as human and animal presence and temperature, among other factors). Sampling of snails and water parameters was performed once at each site and no seasonal differences were considered which, of course, is an important shortcoming. Data on snail distribution in areas with low population densities are missing due to the sampling strategy that was based on human-inhabited areas and our focus on water sites where human activities take place. However, since snail abundance has been previously found to be higher where human water contact takes place, this does not present a limitation (Madsen et al., 1992). Future research to establish seasonal dynamics of snail distribution and monitor infection rates of the snails in the Tchologo region is warranted and, indeed forms part of the recently launched SCORE project.

The work presented here established the potential occurrence of spatial and temporal distribution patterns of snails that are of medical importance in the Tchologo region and can help researchers, disease control managers and the national schistosomiasis control programme to assess potential risk areas in need for preventive chemotherapy coupled with targeted snail control.

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10. Discussion:

10.1 From innovation to application

In the aim to fight and ultimately eliminate neglected tropical diseases in general and schistosomiasis, but also human fascioliasis, in particular, progress is needed pertaining to all stages of innovation, validation and application of new tools, research and control strategies around schistosomiasis (Utzinger et al., 2011; WHO, 2012a; Rollinson et al., 2013b).

Chapters from this thesis pertain mostly to innovation and validation. Innovation in the sense of knowledge creation around prevailing social and ecological factors in the study area in northern Côte d'Ivoire interrelated with disease occurrence but also in the sense of working towards improving and facilitating the practical implementation of methodological concepts for the conduction of scientific studies; validation in the on-going examination of test performing in the various settings where our research took place. An overview on where each chapter of this thesis is placed within the scale from innovation to application can be seen in table 9.1.

Table 10.1 Placement of the thesis chapters in the frame from innovation to application

Chapter	Title	Innovation	Validation	Application
4	A guide to household sampling in the field: computer simulated comparison and review of the literature	Existing household sampling methods in the field are summarized and new methods improving the sampling are proposed	Existing and newly proposed methods for household sampling are validated using a computer simulated sampling and subsequent comparison of the resulting sample.	
5	All that is blood is not schistosomiasis: considerations for the use of reagent strip testing for urogenital schistosomiasis with special consideration to very low prevalence settings		The usefulness of reagent strip testing for microhaematuria as a proxy for <i>S. haematobium</i> infections is discussed in the context of different prevalence settings and the potential occurrence of alternative causes for microhaematuria	
6	Validation of a point-of-care circulating cathodic antigen urine test for <i>Schistosoma mansoni</i> diagnosis in the Sahel and potential cross-reaction with pregnancy		Evaluation of the test performance of the POC-CCA for application in extreme conditions as well as potential cross reaction in pregnancy	
7	Access to, and use of, water by populations living in a schistosomiasis and fascioliasis co-endemic area of northern Côte d'Ivoire	First evaluation of water contact patterns as well as the reasons for using specific water sources in northern Côte d'Ivoire.		
8	Distribution of Schistosomiasis and fascioliasis intermediate host snails on the Tchologo region in northern Côte d'Ivoire	Establishing a model for the distribution of intermediate host snails for schistosomiasis and fascioliasis as well as important environmental factors in northern Côte d'Ivoire		
10	Discussion			Discussing considerations for the application of knowledge in health-interventions using social marketing

10.2 Towards a more holistic systems view of the interrelation between snail-borne trematodiasis and the health and wellbeing of populations

In the fight against neglected tropical diseases in general, and snail-borne trematodiasis in particular, it would be of great advantage to employ a more holistic, systems view of the complex interrelating factors contributing to the distribution patterns of the diseases considering all aspects from methodological aspects in research and health assessment to social ecological considerations in the complex interplay of factors leading to health and disease.

10.2.1 Disease detection

If we truly aim for elimination of schistosomiasis, a few things are needed. First of all, we need to improve the diagnostic tools that we have and invent new ones. As Utzinger et al (2011) states, the need for accurate diagnosis cannot be overemphasized (Utzinger et al., 2011). The point-of-care circulating cathodic antigen test for *S. mansoni* is one promising diagnostic tool, easy to implement in the difficult setting of resource-constraint developing countries (Van Dam et al., 2004a; Colley et al., 2014; Bergquist et al., 2015). It does not need any laboratory equipment and staff can be rapidly trained to use it. *POC-CCA* test cassettes are easy to handle and interpret. Our work in Chad and Côte d'Ivoire contributes to the further validation of the diagnostic assays as it included *POC-CCA* test cassettes for the testing of *S. mansoni* infections. This enabled us to validate the usefulness of this diagnostic tool in very harsh environmental conditions as present on the Sahel zone where ambient temperatures often rise above 40°C. However, *S. mansoni* prevalences in our study settings were very low. Only 13 *POC-CCA* tests in the Chadian setting and none in the Ivorian setting delivered a positive result. We therefore cannot give an answer to the question of whether or not the *POC-CCA* test results would be equally reliable in this setting compared to less harsh conditions. To answer this question, an experimental test-setup would be needed which would

ideally be testing the same samples in two different conditions, once in the harsh field-conditions and once, for example, in an air-conditioned laboratory environment.

One interesting and important finding concerning the *POC-CCA* test cassette pertains to the possibility of a cross reaction in pregnancy. While the number of confirmed pregnancies in the sample was small, performing the test with a pregnant, Swiss individual with no history of exposure to *S. mansoni* revealed a positive test result. Yet, not all pregnant individuals in the sample tested positive with the *POC-CCA* assay. Indeed, another pregnant Swiss individual with a history of travels to schistosomiasis endemic countries did have a negative *POC-CCA* test result. Further research is needed to confirm a possible cross-reactivity of the *POC-CCA* test in pregnant women and to elucidate exactly which factors in pregnancy leads to a positive test, for example, whether it is linked to a specific pregnancy phase.

Another widely used diagnostic tool, but for the assessment of *S. haematobium* prevalence, is the detection of microhaematuria in urine using reagent strips. Several reviews have repeatedly confirmed the usefulness of reagent strip testing in *S. haematobium* diagnosis (King and Bertsch, 2013; Ochodo et al., 2015). However, the test does not directly screen for *S. haematobium* but for commonly related morbidity which can also have other causes such as urinary tract infections or even sickle cell anaemia (Benbassat et al., 1996; Tomson and Porter, 2002; McDonald et al., 2006). Our research indicated that in most published surveys there was at least some microhaematuria detected with reagent strips microhaematuria (on average 13%) that does not relate to *S. haematobium* infection as detected through urine filtration. This finding was irrespective of underlying prevalence (as determined by urine filtration) and whether the study was performed before or after treatment. In post-treatment studies we would arguably expect that only very few positive reagent strip results with negative filtration would be due to missed cases of *S. haematobium* and that there are indeed other causes of microhaematuria. However, as a reviewer of the respective chapter correctly pointed out to us, cure rates with praziquantel can be as low as 50% and the number of missed cases could therefore be considerably higher (King et al., 2000; Liu et al., 2011). These considerations now have two important implications for the fight towards elimination of schistosomiasis. First, if we

assume that other causes of microhaematuria are present, the need for new, direct diagnostic tools with sensitivity higher than the one for urine filtration and specificity higher than for reagent strip testing becomes even more evident to avoid misdiagnosis and unnecessarily treating individuals tested with reagent strips.

If, however, the second assumption that the positive reagent strip tests should genuinely be attributed to missed *S. haematobium* infections holds true, it would mean that many settings classified as low-prevalence indeed show higher prevalences than previously assumed and that our control measures worked less well than we assumed.

To find out which of the assumptions holds true, an assessment of microhaematuria in areas not endemic for *S. haematobium* might be helpful in understanding whether alternative causes for microhaematuria frequently occur. Yet, findings from a *S. haematobium* free setting will most probably not be generalizable to *S. haematobium* endemic areas. The main conclusion in both cases, however, remains virtually the same. A better, more reliable diagnostic test is needed also for *S. haematobium*. there are some valid tools ranging from rapid assessment with questionnaires to elaborate PCR-based diagnostic methods, but the work to find a cheap, easy to use diagnostic tool with high sensitivity and specificity for the use in difficult resource-constrained field settings continues (Cabada and White, 2012; Gomes et al., 2014; Utzinger et al., 2015). The choice of diagnostic tools to be used in a given setting must reflect the context in which they are being used. A setting with high infection numbers and intensities calls for a rapid assessment tool and a quantitative method to assess disease burden. Whereas in an elimination setting with only a few remaining infected individuals, needs highly sensitive diagnostic tools to ensure proper identification and treatment of infected subject.

The diagnosis of human fascioliasis faces even more severe shortcomings. Egg detection in stool remains the most common diagnostic approach for fascioliasis in developing countries. However, the latent phase of fascioliasis can last for months and even in the chronic phase flukes can cease to excrete eggs. Furthermore, the passing of eggs ingested through infected meat but non-infectious for humans can lead to a false positive test result in humans. Some immuno-assays have been

developed but so far they remain rather expensive and difficult to use (Cabán-Hernández et al., 2014; Mas-Coma et al., 2014b). Additionally the lack of awareness of fascioliasis as an important human disease further contributes to the neglecting of this snail-borne trematode despite its world-wide distribution (Mas-Coma et al., 2009).

10.2.2 Climate and ecology

The hardest to control factors in the snail-borne infections system concerns the ecological and abiotic factors influencing the disease. Schistosomiasis and fascioliasis and their respective intermediate snail hosts, are extremely dependent on the occurrence of certain ecological factors (King, 2010; Adema et al., 2012). A suitable water body has to be available harbouring suitable intermediate snail hosts. In our work we could confirm the presence of several schistosomiasis and fascioliasis intermediate host snails in the Tchologo region in northern Côte d'Ivoire and shed light on the prevailing abiotic and ecological factors interacting with snail presence. Snail control has been a feature in some control programmes but due to complex ecological and social interrelations, it remains a very difficult feature (Takougang et al., 2007; King and Bertsch, 2015). Removing an organism such as the intermediate host snail from an established, balanced eco-system is never trivial and the ecological consequences are difficult to foresee (Shiff and Garnett, 1961; Levin, 1998). The use of molluscicides such as niclosamide and copper sulfate can also affect other water organisms which could, in turn, disrupt an eco-system (Shiff and Garnett, 1961; Takougang et al., 2007).

Climate change is an important factor altering the currently known distribution of host snails as well as the abiotic factors leading to the survival of the cercaries in water bodies previously free of *Schistosoma* species (Gajadhar and Allen, 2004; Macpherson, 2005; Mas-Coma et al., 2009). Intermediate host snails transmitting human schistosomiasis generally occur in water with a temperature higher than 25 degrees (Shiff, 1964; Appleton, 1978). The (re-)emergence of *S. haematobium* infections acquired in Corsica, France, has led to some concerns about this issue.

Furthermore, possible reservoir host species for schistosomiasis and fascioliasis including primates, domestic ruminants and even rodents, exist and reaching them with interventions is impossible (Nithiuthai et al., 2004; Wang, 2005). This further complicates the already complex fight towards elimination or even eradication of diseases such as schistosomiasis and fascioliasis (Prichard et al., 2012; Zhou et al., 2012).

10.2.3 Social, cultural and anthropomorphic factors

Tightly interlinked with the aforementioned ecological factors, are social determinants of the distribution of snail-borne trematodes. Individual behaviours, beliefs and the extent of contact with contaminated water greatly determines the risk of infection for individuals (Useh and Ejezie, 1999; Macpherson, 2005; Chomel, 2008; Utzinger et al., 2011). So does the supply with safe drinking water and sanitation and hygiene facilities. These issues have been extensively discussed in the literature although they are still inexcusably neglected (Huang and Manderson, 1992; Useh and Ejezie, 1999; Nithiuthai et al., 2004; Macpherson, 2005). There is, however, one additional consideration derived from our work on the access to, and use of, water sources in northern Côte d'Ivoire. The vast majority of water contact and water consumption, as well as a great deal of sanitation and hygiene behaviours take place at the place of work, which was in many cases at agricultural fields and the roadsides for trade. These locations have to be included in intervention programmes. While safe facilities in the villages and homes are a great asset, their availability seems to not be the only issue determining their exclusive use. Sufficient quantities of drinking water may not be transportable all the way to the work place and adequate sanitation facilities are even more difficult to provide far from the living place. Coming up with solutions for this problem will be difficult but it is evident that it will play a crucial role in the fight towards elimination of snail-borne diseases. Physical contact with water cannot be eliminated since open water sources are vital for agriculture and various other needs. However, during our work we found that even individuals who otherwise use only safe water, rendered into contact with open

water through the crossing of streams and other water bodies (Krauth et al., 2015a). Such crossing exposes individuals to possible infections with schistosomiasis (Grimes et al., 2015). The construction of roads and bridges might be part of the solution in areas where control measures are more advanced. Development of infrastructure apart from the supply of safe water and adequate sanitation facilities could therefore have an additional positive impact on the health of people. On the other hand, anthropomorphic changes of the environment comprising the construction of Dams for various purposes, can further increase host-snail distribution and thereby infection risk (Ross et al., 2002; Steinmann et al., 2006b; Mas-Coma et al., 2009)

During our work with the local populations we learned that, the increasing national and international trade has led to an increase of agricultural fields in the northern region of Côte d'Ivoire. These new agricultural fields in the Tchologo region have, in some cases, substantially altered the water access of semi-nomadic cattle herder's and their animals (data not shown). Formerly used water points are now no longer accessible to the cattle herds due to the economic consequences for the herders if the cattle destroy the fields. New routes for grazing cattle had to be established including the use of different watering sites. In some cases we were told that the herders had to access certain water sites despite the fact that they knew the cattle frequently got sick from them. Employing a one-health approach could, on one side, enable interventions to tackle issues related to animal and human impacts at the same time. A one-health approach could thus be important not only for the treatment and prevention of illness, but also already in the research itself, which has been attempted during the present work by the tight collaboration between several PhD candidates working on animal-related and human-related research questions that are, to a large extent, interrelated.

Tapping into the same relations, are intercultural differences between the sedentary village population and the semi-nomadic Peulh population related to different exposures and subsequent risk of infection. First of all, in the northern region of Côte d'Ivoire individuals of the Peulh ethnicity are the once taking care of animal herds, including the herds belonging to villagers (Bassett, 1994). Through

accompanying the cattle herds, the herders access water bodies, which are too far away for children from the villages to swim in (data not shown). Additionally, many Peulhs live in small camps outside of the villages. Therefore, the semi-nomadic Peulh population has a substantially different access to water sources compared to the village population. Not only do they report to often have to pay a fee for accessing the village's wells, water pumps or other safe water sources, their camps are also not listed on any administrative record and the risk is therefore great that this part of the population group is excluded from any intervention programmes.

This is further worsened by the current practice of targeting schools for treatment programmes and mass-drug administration. Non-solarised children are systematically excluded from treatment programmes (Woolhouse, 1998; Anderson et al., 2013) even when school-children are asked to invite other children not enrolled in school, this would not necessary lead to the inclusion of children from camps living outside of the villages.

10.2.4 Globalisation

The massive increase in worldwide mobility and international trade of food and livestock contributes to the spread of host-snails as well as the parasites themselves (Gajadhar and Allen, 2004; Mas-Coma, 2005). Another, less obvious influence of the global trade and globalisation, pertains to the easy and cheap availability of generic anthelmintic drugs. While many real generic brands do contain the required amount of the active compound, more and more counterfeit and poor-quality drugs exist which often don't contain enough of the active compound. Yet for financial reasons, people often refer to them for treatment (Sulaiman et al.; Pécoul et al., 1999). Economic factors therefore also play a role in the complex system of interrelations between humans and snail-borne trematode diseases. It is well-known that schistosomiasis disproportionally affects the poor population having little access to safe water and sanitation and hygiene factors (Uttinger et al., 2011; Uttinger et al., 2012). These economically disadvantaged population groups then often can not afford medical examination or treatment and remain infected. To make matters

worse, the reduced cognitive and physical ability further leads to further economic disadvantages due to worse performances in school and during work (King, 2010).

10.2.5 Politics and education

Political decisions on a global as well as a local level have direct impact on the health and wellbeing of populations. Health education, for one, is an important factor in the fight towards neglected tropical diseases and large efforts are put into educational programmes by international donors (Kloos, 1995; WHO, 2002a; Asaolu and Ofoezie, 2003). However, political decisions outside of the health ministries can influence education efforts. During our work, we heard from one of the teachers we worked with that they no longer teach details about schistosomiasis in their school and that she had believed this was because the disease no longer existed in the country. This finding was concurrent with the perception by other participants, which either had not heard about schistosomiasis or thought schistosomiasis to be a child disease of no importance to adults (data not shown). Adequate health education is not only important to enable people to avoid risk contact but also to understand the disease and the potential for infection from adults as well.

Other political decision influencing neglected tropical diseases concern the allocation of necessary funding to the fight of diseases and the strengthening of health systems. On one hand, international donors tend to prefer funding national surveys and vertical, single-disease approaches instead of investing in the general establishment and strengthening of well-functioning health systems (Bergquist et al., 2015), on the other hand not enough resources are being put into the production of needed drugs against schistosomiasis and even less financial resources are allocated to the fight against human fascioliasis (Chomel, 2008; Hotez et al., 2010; WHO, 2013b; Lai et al., 2015).

10.2.6 Methodological considerations

One consideration within this PhD Thesis covers the aspect of improving knowledge generation itself through the improvement of data collection methodological aspects.

In this work, we specifically focused on the selection of households for inclusion in epidemiological and other research surveys. To the best of our knowledge, little attention is given to developing new scientific methods or improving existing ones, despite the acknowledged relationship between a good, representative sample of the population and the usefulness of collected data (Fowler, 2013; Levy and Lemeshow, 2013). Depending on the ultimate aim of any survey, a sample should ideally be representative of the population under study. We therefore validated published methods of in-field household sampling methods and proposed some new variations of current strategies. Special consideration is given to easy implementation in the reality of the field while trying to avoid the systematic exclusion of households from the sample. These tools can help researchers perform high quality research. However, in the end the performance of any research and any intervention depends in large parts on the dedication and adequate training of all people involved as well as good leadership and management.

Another methodological potential in the fight against single diseases, is the integration of control or elimination efforts of one disease with those targeting other diseases and development issues. The benefits of such integrated control measures are well known (Molyneux et al., 2005; Brady et al., 2006; Utzinger et al., 2009a). To effectively fight against neglected tropical diseases and achieve elimination of schistosomiasis, we need to get away from the simple one-disease one-fight view and work towards systems thinking, health-systems strengthening, transdisciplinary work, and integrated control.

10.2.7 Efficient application of research findings and the case for social marketing

One part often a bit neglected is the application of the research findings into practical intervention programmes. The nature of this work and the involvement of many stakeholders makes the application of knowledge sometimes slightly tricky. Nevertheless, once generated and validated, knowledge must be disseminated and translated into action. This highly complicated matter often involves working together

with politics, economists, various stakeholders as well as the actual target population itself and goes beyond the work performed at a research institution. Nevertheless, researchers should not cease to be interested in these matters merely because their research has been done. Firstly, scientific experts are needed to inform and counsel decision makers and non-governmental organizations on scientific advances and findings in order for them to be translated into actions. Secondly, once designed and running, intervention programmes and control strategies need to be constantly evaluated for their efficiency and efficacy.

In any intervention programmes targeted at changing behaviours, community participation as well as ownership and strong identification with the cause at hand, is key to the successful implementation of health interventions. As has been shown in the case of community lead total sanitation, community participation, ownership and pride lead to successful and long lasting adoption of behavioural and structural changes which contribute towards the improvement of the general health of a community (Useh and Ejezie, 1999; Kar and Chambers, 2008; Chambers, 2009; Harvey, 2011). This crucial sociological component is the reason why programmes aiming to implement research findings and transfer knowledge into action, can greatly benefit from working together with social marketing concepts and experts. The study of what makes human act and how to influence these behaviours has been part of the fields of social psychology and (social) marketing. Interdisciplinary and transdisciplinary collaboration sociologists and anthropologists has already enabled researchers to adopt more people centered view of health related issues and can help us understanding the reality of the affected populations (Hahn and Inhorn, 2009). Human behaviour is guided by extremely complex interplays of external and internal social and psychological factors (Strack and Deutsch, 2004). Understanding the mechanisms which lead to the adoption of desired behaviours and subsequently translating these principles into control strategies seems complicated at first sight but could greatly increase the success of an intervention.

Mostly employed in highly functioning, developed health systems, social marketing uses a combination of in-depth audience analysis and marketing strategies plus long-term follow up to successfully convey health messages and

maximises the adoption potential in the target population. By tailoring health interventions and their messages to the population, their needs and concerns, interventions can have a broader impact. In order to achieve this, simple fear messages telling people why a certain behaviour is bad for their health and can have negative impacts have to be replaced by messages evoking stronger emotional reactions, triggering a desire to adopt the wanted behaviour. Social marketing tries to focus their communication on issues that are important to the local population and that harbour an internal incentive to adopt and keep the behavioural change in the long run. Most importantly, before designing an intervention, social marketing focuses first on the analysis of the issue at hand with all its complexity before attempting to come up with a possible solution. When interventions are planned, it is important to fully understand which population segment you are exactly trying to reach, what are their concerns and priorities and makes people act.

Examples of successful social marketing campaigns on public health issues include a programme aiming to increase hand-washing behaviour in nurses in order to minimise the spread of hospital-acquired infections in patients which focused on the self-protection of the nurses rather than the actual concern for the patients (Conway and Langley, 2013) and a nutrition program in Texas aimed at women, infants and children which increased their reach by changing people's perception of the programme from a charitable organization to an education platform for everyone, taking into account the families' pride and self-perception (Grier and Bryant, 2005). Social marketing has been shown to work with a variety of target populations from the general population to health practitioners and decision makers (Gordon et al., 2006). It can also take into account in which state the intervention is in a given setting. There is a difference in the approach whether one aims at reaching the first adopters of a specific behavioural change or the very last few people that have not yet been reached. "Competition for attention" between various social, political and public health causes is another important consideration, which once again tabs into the issue of integrated control programmes.

Key informants such as village leaders or other influential persons are identified and engaged in bringing about the behavioural changes desired. (Grier and Bryant,

2005; Gordon et al., 2006). All these factors need to be considered during the design and implementation of a health intervention, all the while not jumping to quick solutions that sound good in theory but sometimes just do not seem to catch on in reality.

10.3 Conclusions

A holistic view on the entire system of determinants for disease and health is an important approach especially when dealing with complex interrelated diseases such as snail born trematodes. A myriad of factors from biological, ecological and social aspects to human behaviour, economics and politics play a role in the distribution of infection. In the run for elimination, however, also methodological considerations will be an important denominator for success or failure. The further we get, the more reliable and rigorous the diagnostic methods and treatment options need to become. But also, the very methods with which we assess the success or failure of a programme have to be evaluated and improved to ensure reliable data about remaining infections and issues. By working together in an interdisciplinary and transdisciplinary way with various scientific fields but also with stakeholders, authorities and, most importantly, the affected general population itself, we increase our chances to indeed be able to achieve elimination of the most prevalent snail-borne disease, schistosomiasis, from several areas.

10.4 Identified research needs

As a last point, there is the obvious, countless-times repeated conclusion of “further research is needed”. Despite it being the subject of many a joke (Unconscious, 2013), rigorous scientific research is key in trying to explain the world and keeping up to date with the complex interrelations of any disease system. As progress is being made with health interventions and prevalences decrease, new determining factors for the spread of snail-borne infections may become important, which had formerly been hidden among other, more prevalent, factors yet gain in relative importance once other factors have been addressed. Continued high-quality research is therefore still of great importance at the end of each research.

Some further research needs, which were identified during the work on this doctoral thesis, include:

- Better diagnostic methods for urinary and intestinal schistosomiasis are needed especially in very low prevalence settings where the well-known limitations of currently existing tools preponderate.
- Research on human fascioliasis in general should be greatly increased. Currently only little effort is being made despite the widespread distribution of the disease.
- Our findings of near equal levels of “false positive” reagent strip tests for microhaematuria in many international studies on schistosomiasis, raises the question whether, and to what extent, alternative causes for microhaematuria exist in these settings. Alternative causes for microhaematuria can be an important health issue that gains in relative medical importance when schistosomiasis can be ruled out as a cause.
- The complex interrelation between culture and social factors of snail-borne infections should be assessed in more depth. Indeed, data on the issue of differences between the local village population and the Peulh population, mostly living outside the villages, have been collected and work on this aspect of the systems epidemiology will continue after the completion of this thesis.
- Further work will be done on the evaluation and improvement of household sampling methods to come up with a method that performs closer to a simple random sample.
- The amount of infection in host snails in the northern part of Côte d’Ivoire should be assessed in order to get further insight in the potential distribution of schistosomiasis and fascioliasis in the area.
- The supply of water and adequate sanitation has long been recognized as a crucial factor in the fight against neglected tropical diseases. However, some effort should be directed at the problem of water supply and sanitation on the workplace of people, especially around agricultural fields. This is a complicated issue not as easily solved as water and sanitation supply at the living place, but seeing that people spend a large part of the day working on the fields, it is a huge factor contributing to the risk of infection.

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- Thought should be given to the problem of crossing water bodies as a remaining potential exposure to schistosomiasis in people who otherwise only use improved water sources.

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11. Curriculum Vitae

Personal information

Name: Stefanie Jennifer
Surname: Krauth
Date of birth: 15 June 1985
Nationality: Germany
E-Mail: stefanie.j.krauth@gmail.com

Research interests

Inter- & transdisciplinary scientific work towards improving the lives and health of humans, animals and the ecology

Academic education

04/2012 – **PhD in Epidemiology**, Swiss Topical and Public Health Institute (Swiss
09/2015 TPH), University of Basel, Switzerland
PHD Thesis Title: *“Systems epidemiology of snail-borne diseases: from methodological to social-ecological considerations in the fight towards elimination”*

04/2012 – **PhD Program in Public Health** of the Swiss school of Public Health
09/2015 (SSPH+)

09/2009 – **Master of Science in Infection Biology and Epidemiology**; Major in
02/2011 Epidemiology, Swiss TPH, University of Basel, Switzerland
Master Thesis Title: *“Current field procedures for the diagnosis of helminth infections: effect of homogenization, time delays and storing methods on faecal egg count variation”*

09/2006 – **Bachelor of Science in Biology**; Major in Integrative Biology, University
07/2009 of Basel, Switzerland

Curriculum vitae

Work experience abroad

Total of >1 year in-country experience for various projects in three different settings in Côte d'Ivoire ● working with multi-lingual teams from various cultural, ethnic and religious backgrounds in urban and remote areas ● working in formerly rebel-held areas and in pre-, and post-war situations ● working with limited resources.

Practical skills and advanced training

Technical skills & additional training: ● Study design and implementation ● data collection & analysis ● mixed methods research ● interdisciplinary and transdisciplinary working ● designing and conducting interview surveys, focus group discussions and direct observations ● methods development & validation ● Laboratory work around helminth infections ● proposal writing (project-, ethical- & grant proposals) ● conducting fieldwork (incl. developing countries) ● handling of potentially infectious human samples ● writing and publishing peer reviewed articles ● very good oral presentation skills ● Good clinical practice (1d training) ● qualitative research methods (course) ● United nations basic security in the field & advanced security in the field (certificates)

Project management & leadership: ● student supervision (two M.Sc., from project definition to completion) ● leading, managing and motivation of field investigators and technicians ● organisation and execution of scientific events and conferences ● good knowledge of ethics in research (*best semester work in ethics on informed consent in the context of social need*) ● Formal training in leadership and communication

Interpersonal skills: ● collaborative work with international institutions, local authorities, and the general public ● good communication among complex teams of researchers, local authorities and other partners from different backgrounds ● very quick learning abilities ● history of successful teamwork leading to several co-authored publications

Curriculum vitae

Computer skills

STATA, Endnote, EPI Info, Open Data Kit (ODK), GIMP, Prezi, Cmap tools, Microsoft Office (Word, Power Point, Excel), Vensim, Zotero

Language skills

German: Expert, mother tongue
English: Expert (C2)
French: Oral: advanced (C1)
Written: intermediate (B1-B2)

Publications

1. Stefanie J. Krauth & Nathalie Wandel, Seïdinan I. Traoré, Penelope Vounatsou, Jan Hattendorf, Louise Y. Achi, Kristopher McNeill, Eliézer K. N'Goran, Jürg Utzinger (2016) **Distribution of intermediate host snails of schistosomiasis and fascioliasis in relation to environmental factors during the dry season in the Tchologo region, Côte d'Ivoire**, *Advances in Water Resources* (2016)
2. Helena Greter, Stefanie J. Krauth, Bongo N. R. Ngandolo, Idriss O. Alfaroukh, Jakob Zinsstag & Jürg Utzinger (2016) **Validation of a point-of-care circulating antigen urine cassette test for *Schistosoma mansoni* diagnosis in the Sahel, and potential cross-reaction with pregnancy**, *American Journal of Tropical Medicine and Hygiene*, 94(2) 361-364
3. Stefanie J. Krauth, Helena Greter, Katarina Stete, Jean T. Coulibaly, Seïdinan I. Traoré, Bongo N. R. Ngandolo, Louise Y. Achi, Jakob Zinsstag, Eliézer K. N'Goran & Jürg Utzinger (2015) **All that is blood is not schistosomiasis: experiences with reagent strip testing for urogenital schistosomiasis with special consideration to very-low prevalence settings**, *Parasites & Vectors*, **8**: 584
4. Stefanie J. Krauth & Capucine C. Musard, Seïdinan I. Taoré, Jakob Zinsstag, Louise Y. Achi, Eliézer K. N'Goran & Jürg Utzinger (2015) **Access to, and use of, water by populations living in a schistosomiasis and fascioliasis co-endemic area of Côte d'Ivoire**, *Acta Tropica* **149**: 179-85
5. Peiling Yap, Fang-Wei Wu, Zun-Wei Du, Jan Hattendorf, Ran Chen, Jin-Yong Jiang, Susi Kriemler, Stefanie J. Krauth, Xiao-Nong Zhou, Jürg Utzinger, Peter Steinmann (2014). **Effect of deworming on physical fitness of school-aged children in Yunnan, China: a double-blind, randomized, placebo-controlled trial**. *PLoS neglected tropical diseases* **8** (7), e2983
6. Stefanie J. Krauth, Jean T. Coulibaly, Stefanie Knopp, Mahamadou Traoré, Eliézer K. N'Goran, Jürg Utzinger (2012). **An in-depth analysis of a piece of shit: distribution of *Schistosoma mansoni* and hookworm eggs in human stool**. *PLoS Neglected Tropical Diseases* **6**: e1969. (Most viewed article in PLoS NTD, Recommended by the faculty 1000 Prime)

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7. Katarina Stete, Stefanie J. Krauth, Jean Coulibaly, Stefanie Knopp, Jan Hattendorf, Ivan Müller, Laurent K. Lohourignon, Winfred V. Kern, Eliézer K. N’Goran & Jürg Utzinger (2012). **Dynamics of *Schistosoma haematobium* egg output and associated infection parameters following treatment with praziquantel in schoolchildren.** *Parasites & Vectors* **5**: 298.
8. Ivan Müller, Jean T. Coulibaly, Thomas Fürst, Stefanie Knopp, Jan Hattendorf, Stefanie J. Krauth, Katarina Stete, Aurélie A. Righetti, Dominik Glinz, Adrien K. Yao, Uwe Pühse, Eliézer K. N’Goran & Jürg Utzinger (2011). **Effect of schistosomiasis and soil-transmitted helminth infections on physical fitness of school children in Côte d’Ivoire.** *PLoS Neglected Tropical Diseases* **5**: e1239.
9. Jürg Utzinger, Laura Rinaldi, John B. Malone, Stefanie J. Krauth, Thomas K. Kristensen, Giuseppe Cringoli & Robert Bergquist (2011). **Geospatial Health: the first five years,** *Geospatial Health* **6**, 137-154
10. Stefanie J. Krauth (2011) **Current field procedures for the diagnosis of helminth infections: effect of homogenization, time delays and storing methods on fecal egg count variation.** MSc thesis, University of Basel, Switzerland & Swiss Tropical and Public Health Institute, Basel, Switzerland (*MSc thesis*)

- Conferences** 20th Symposium of Biology Students in Europe (SymBioSE); Lund, Sweden; 24.07-31.07.2017, **workshop**
- 19th Symposium of Biology Students in Europe (SymBioSE); Lisbon & Vila Real, Portugal; 27.07-05.08.2016, **workshop and poster, people’s choice for best poster**
- 9th European Congress on Tropical Medicine and International Health 06.-10-09-2015, Switzerland, **poster presentation**
- 9th International Symposium on Geospatial Health, Basel, Switzerland, 05-06.09.2015, **local organizing committee & participant**
- 18th Symposium of Biology Students in Europe (SymBioSE); Alexandroupolis, Greece; 23-31.07.2015, **participant**
- 3rd international One Health Congress, Amsterdam, the Netherlands, 15–18.03.2015; **oral presentation, special prize for best oral presentation**
- Winter Symposium of Biology Students in Europe, Arandjelovac, Serbia, 02-08.02.2014, **participant**
- Environment and Health – Bridging South, North, East and West, Conference of ISEE, ISES and ISIAQ, Basel, Switzerland, 19-23.08.2013, **working experience**
- 17th Symposium of Biology Students in Europe (SymBioSE); Sheffield, England; 18.07-01.08.2013, **oral presentation**

Curriculum vitae

16th Symposium of Biology Students in Europe (SymBioSE); Szeged, Hungary; 26.07-05.8.2012, **oral presentation & workshop**

15th Symposium of Biology Students in Europe (SymBioSE); Basel, Switzerland, 27.07-06.08.2011, **core organizer & participant**

Additional experiences and associations

- 09/2015 **Local organizing committee member**, 9th International Symposium on Geospatial Health, Basel, Switzerland, 05 - 06.09.2015 (~40 participants): Administrative work, organization of infrastructure and catering, help desk
- 08/2013 **Conference working experience**, Environment and Health Conference of ISEE, ISES and ISIAQ, Basel, Switzerland, 19 – 23 August 2013 (1700 participants): participant registration, Support desk, information desk, trouble shooting and problem solving for participants
- 02/2006 - **Executive board member** of the association of biology students of the University of
- 03/2014 Basel, **Presidency from 09/2006 to 04/2010**
- 06/2011 - **Chair** of the Student's Research Seminar of the Swiss Tropical and Public Health
- 06/2012 institute (Swiss TPH) in Basel, Switzerland
- 10/2009 - **Core organizer** of the Symposium for Biology Students in Europe
- 08/2011 (SymBioSE), Switzerland, July 27 – August 6, 2011, (~ 100 participants), Event organization without core funding, main task: communication with, and relations to, the university of Basel and associated research institutions, coordination of meetings, scientific and cultural programme, participants coordination

Basel, 05.07.2017



(Stefanie J. Krauth)