

Epidemiology, spatial distribution and control of schistosomiasis mansoni in western Côte d'Ivoire

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Summary

Background: Preventive chemotherapy is a strategy of delivering anthelmintic drugs to people at-risk of schistosomiasis without prior diagnosis. Currently, World Health Organization (WHO) recommends this strategy for morbidity control targeting six major helminthiases among the 17 neglected tropical diseases (NTDs) which pose a considerable public health problem and impair the economic development of tropic and sub-tropical countries. Among these helminthiases, schistosomiasis affects more than 250 million people, mainly in sub-Saharan Africa. Since the mid-1980s, preventive chemotherapy with praziquantel has been advocated by WHO for schistosomiasis control. It is believed that high-coverage of preventive chemotherapy in endemic settings not only prevents morbidity and long-term sequelae of schistosomiasis, but might also interrupt the transmission of the disease. The present WHO goal for schistosomiasis morbidity control is to regularly reach at least 75% and up to 100% of school-aged children in endemic areas. This ambitious target was supported by international donors and pharmaceutical companies who decided to offer praziquantel tablets free of charge to endemic countries. While, preventive chemotherapy with praziquantel is being scaled up there are several concerns, such as treatment failure to clear infection, development and spread of drug resistance, low drug coverage particularly after several years of administration, lack of baseline data for better assessment of the treatment impact and sustainability of this strategy.

Goal and specific objectives: The overarching goal of this Ph.D. thesis was to deepen our understanding of the epidemiology and spatial distribution of schistosomiasis mansoni in four regions of western Côte d'Ivoire, and to assess the impact of preventive chemotherapy with praziquantel on schistosomiasis one-year post-treatment. The study was readily integrated into a multi-country investigation financed by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE). This thesis pursued four specific objectives. First, to contribute to the design of a study protocol with the aim to sustain the control of *Schistosoma mansoni* in moderate endemicity areas (prevalence of infection of baseline: 10-24%). Second, to map and predict the spatial distribution of *S. mansoni* in the western part of Côte d'Ivoire. Third, to determine the baseline parasitological and social-ecological situation of local communities before the implementation of a randomised controlled trial to sustain schistosomiasis mansoni control. Fourth, to assess the impact of preventive chemotherapy with praziquantel on the prevalence and intensity of *S. mansoni* and to determine the dynamics of infection one year after the treatment intervention.

Methods: The field work for this Ph.D. was split into three parts: eligibility, baseline and one-year post-treatment surveys. The eligibility survey took place from June to August 2011 and in December 2011. School-based cross-sectional parasitological surveys were conducted in Cavally, Guemon, Tonkpi, and Haut-Sassandra, regions of western Côte d'Ivoire. Around 50 children aged 13-14 years per school were screened for *S. mansoni* infection using duplicate Kato-Katz thick smears. 75 schools with *S. mansoni* prevalence ranging between 10% and 24% were selected for a more detailed baseline survey and randomised to one of three treatment arms (A, B and C). Baseline surveys were carried out from December 2011 to February 2012. Approximately 100 children aged 9-12 years per school provided three stool samples on three consecutive days, while a single stool sample was collected from 100 first graders. The stool samples were subjected to the Kato-Katz method (duplicate Kato-Katz thick smears per stool sample) for identification and enumeration of *S. mansoni* eggs. In addition, a questionnaire on socio-demographic and ecological factors that might influence *S. mansoni* transmission was delivered to school directors and village leaders. In June 2012, a combined school- and community-based mass drug administration with praziquantel (single dose of 40 mg/kg) was conducted, targeting school-aged children living in the school catchment areas. Praziquantel treatment was delivered to children by trained school teachers. In May 2013, One-year post-treatment, a survey was conducted in the 50 schools of treatment arms A and B. Approximately, 100 children aged 9- 12 years per school were screened on three consecutive days for *S. mansoni* infection using the Kato-Katz method. The prevalence and intensity of *S. mansoni* infection were compared between the baseline and the one-year follow-up surveys at the respective schools.

Results: At the eligibility survey, 264 schools were screened. The overall prevalence of *S. mansoni* was 39.9%, ranging from 0% to 100% at the unit of the school. High *S. mansoni* prevalence rates were mostly observed in Tonkpi region. Overall, 157 (59.5%) schools had prevalence of *S. mansoni* above 24%, 78 (29.5%) schools had a prevalence ranging between 10% and 24%, while the remaining 29 schools (11.0%) showed prevalences below 10%. Bayesian geostatistical analysis showed that age, sex, altitude and difference between land surface temperature at day and night were significantly correlated with *S. mansoni* infection. Rice cultivation, open defecation, use of traditional pit latrine, use of natural open freshwater bodies for washing and bathing were potential risk factors associated with *S. mansoni* in local communities. At the baseline survey, after considering at least quadruplicate Kato-Katz thick

smears per child, among the 75 schools where the prevalence of *S. mansoni* was moderate in the eligibility survey (10-24%) we found that the prevalence of infection was higher than 24% in 28 schools (37.3%), while it was below 10% in 7 schools (9.3%). At treatment arm level, we found that the *S. mansoni* prevalence of treatment arm C was slightly higher compared to arms A and B. Our data showed that the directly observed treatment coverage was 84.2%. At the unit of the school, we found that coverage of $\geq 75\%$ was achieved in 57 schools (76.0%). One year post-treatment, the overall prevalence of *S. mansoni* in the 50 schools of treatment arms A and B decreased from 19.7% to 12.8%, while the intensity of the infection slightly increased from 94.9 eggs per gram of stool among infected children to 109.3 eggs per gram of stool. The dynamics of prevalence and intensity of *S. mansoni* were heterogeneous.

Conclusion: The understanding of the spatial distribution of schistosomiasis can help decision-makers for better planning disease control. In the frame of this Ph.D., a spatial explicit risk map of *S. mansoni* was generated for the western part of Côte d'Ivoire that was already been used by the national control programme for spatial targeting of control interventions. In addition, the study showed that the classification of communities according to WHO guideline is fragile which calls for a more accurate tool of categorisation of communities based on the schistosomiasis endemicity. The baseline parasitological and social-ecological situation in the villages provided important information for the 4-year cluster-randomised intervention trial founded by SCORE, which will help to determine the best strategies to sustainably control schistosomiasis mansoni. Our results demonstrated that the dynamics of schistosomiasis in the study areas one-year post-treatment was heterogeneous. Thus, on one hand, there is a need to regularly assess the dynamics of schistosomiasis during this SCORE study to deepen our understanding of the dynamics of schistosomiasis transmission, while on the other hand it might be necessary to implement more integrated control interventions to sustain gains made by preventive chemotherapy and more from morbidity control to elimination.

Zusammenfassung

Hintergrund: Die präventive Massenbehandlung von Menschen mit Anthelminthika ohne vorausgehende Diagnose in Gebieten mit hohem Infektionsrisiko für die Bilharziose ist eine vorsorgende Maßnahme. Zurzeit empfiehlt die Weltgesundheitsorganisation (WHO) diese Strategie zur Kontrolle der sechs Hauptwurmerkrankungen unter den 17 sogenannten vernachlässigten Tropenkrankheiten („Neglected tropical diseases“, NTDs), die ein beachtliches Problem der öffentlichen Gesundheit darstellen und die ökonomische Entwicklung in tropischen und sub-tropischen Ländern hemmen.

Innerhalb dieser Wurmerkrankungen betrifft die Bilharziose mehr als 250 Millionen Menschen, vor allem in Afrika südlich der Sahara. Seit Mitte der 80er Jahre empfiehlt die WHO zur Kontrolle der Bilharziose die präventive Massenbehandlung von Risikogruppen mit Praziquantel. Man nimmt an, dass durch eine ausreichende flächendeckende Behandlung in endemischen Gebieten nicht nur die Morbidität und Spätschäden vermindert werden, sondern auch eine Unterbrechung der Übertragung der Krankheit stattfinden kann. Das Ziel der WHO zur Kontrolle der Bilharziose ist im Moment, regelmäßig mindestens 75% bis 100% aller Kinder im Schulalter, die in endemischen Gebieten leben, zu behandeln. Dieses ehrgeizige Ziel wird von internationalen Spendern und Pharmaunternehmen unterstützt, die entschieden haben endemischen Ländern Praziquantel umsonst zur Verfügung zu stellen. Währendem die präventive Massenbehandlung mit Praziquantel ausgeweitet wird, gibt es einige Vorbehalte, wie zum Beispiel das Versagen des Medikaments zur vollständigen Heilung der Infektion, die Entwicklung und Ausbreitung von Resistenzen gegen das Medikament, die geringe Akzeptanz und Flächendeckung bei der Massenbehandlung, speziell nach ein paar Jahren regelmäßiger Entwurmungen, und der Mangel an ursprünglichen Daten, die helfen würden, die Auswirkungen der Behandlungen und die Nachhaltigkeit dieser Strategie abzuschätzen.

Allumfassende und spezifische Ziele: Das allumfassende Ziel dieser Doktorarbeit war unser Verständnis der Epidemiologie und der räumlichen Verteilung der Darm-Bilharziose in vier westlichen Regionen der Elfenbeinküste zu erweitern und zu erfassen, welche Auswirkung die Massenbehandlung mit Praziquantel ein Jahr nach der ersten Behandlung auf das Vorkommen der Bilharziose in Schulkindern hat. Die Studie war Teil einer Untersuchung, die in mehreren Ländern stattfand und von dem Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) finanziert wurde.

Diese Doktorarbeit hatte vier spezifische Ziele. Erstens sollte sie bei dem Entwurf eine

s Studienprotokolls helfen, das zum Ziel hat die Kontrolle der Bilharziose in moderaten Endemiegebieten von *Schistosoma mansoni* (Prävalenzrate der Infektion: 10-24%) nachhaltig zu gestalten. Zweitens sollte sie bei der Erhebung der Ausgangsdaten helfen und die geographische Verteilung von *S. mansoni* Infektionen in der westlichen Elfenbeinküste mit statistischen Modellen vorhersagen und graphisch anhand von Karten darstellen. Drittens sollten der parasitologische Infektionsstatus und der sozioökologische Kontext der lokalen Gemeinschaften erfasst werden, bevor die randomisiert kontrollierte Studie zur Nachhaltigkeit der Kontrolle von *S. mansoni* Infektionen begann. Viertens sollte die Auswirkung einer Massenbehandlung mit Praziquantel auf die Prävalenz und Intensität von *S. mansoni* Infektionen festgestellt werden und die Dynamik der Infektion ein Jahr nach der Behandlung abgeschätzt werden.

Methoden: Die Feldarbeit für diese Doktorarbeit wurde in drei Abschnitte aufgeteilt: die Datenaufnahme zur Abschätzung der Eignung der Studiengebiete, die Erhebung der Ausgangsdaten für die eigentliche Studie, und die Datenaufnahme ein Jahr nach der Behandlung. Die Eignungsstudie fand von Juni bis August 2011 und von Dezember 2011 bis Januar 2012 statt. Parasitologische Querschnittstudien wurden in den Schulen der Regionen Cavally, Guemon, Tonkpi und Haut-Sassandra, in der westlichen Elfenbeinküste durchgeführt. Pro Schule wurden jeweils um die 50 Kinder im Alter von 13-14 Jahren mittels mikroskopischem Befunds von zwei Kato-Katz Ausstrichen auf *S. mansoni* Infektionen untersucht. Im Ganzen wurden 75 Schulen mit einer *S. mansoni* Prävalenz zwischen 10% und 24% für die detailliertere Erhebung der Ausgangsdaten ausgewählt und in einen der drei Behandlungsarme (A, B und C) randomisiert. Die Erhebung der Ausgangsdaten fand von Dezember 2011 bis Februar 2012 statt. In jeder Schule gaben ungefähr 100 Kinder im Alter von 9-12 Jahren an drei Tagen in Folge ihre Stuhlprobe ab, wohingegen von Erstklässlern eine einzelne Stuhlprobe eingesammelt wurde. Die Stuhlproben wurden mit der Kato-Katz Methode untersucht (zwei Ausstriche pro Stuhlprobe), um Eier von *S. mansoni* zu identifizieren und zu zählen. Zusätzlich wurden Schuldirektoren und Dorfoberhäupter mit einem Fragebogen über sozio-ökonomische und ökologische Faktoren interviewt, die die Übertragung von *S. mansoni* beeinflussen könnten. Im Juni 2012 wurde eine Massenbehandlung mit Praziquantel (einmalige Dosis von 40 mg/kg) in Schulen und Gemeinschaften durchgeführt, um Kinder im Schulalter zu erreichen, die in den jeweiligen Schuleinzugsgebieten lebten. Die Praziquantelbehandlung wurde von geschulten Lehrern an die Kinder verabreicht. Im Mai 2013, ein Jahr nach der Behandlung, wurde eine

Evaluierungsstudie in den Schulen der Studienarme A und B durchgeführt. Hierbei wurden pro Schule ungefähr 100 Kinder im Alter von 9-12 Jahren an drei aufeinanderfolgenden Tagen mit der Kato-Katz Methode auf eine *S. mansoni* Infektion untersucht. Für jede Schule wurde die Prävalenz und Intensität der *S. mansoni* Infektion zwischen der ursprünglichen Studie und der Studie, die ein Jahr nach der Behandlung durchgeführt wurde, verglichen.

Ergebnisse: Im Rahmen der Eignungsstudie wurden 264 Schulen untersucht. Die generelle *S. mansoni* Prävalenz war 39.9%, bewegte sich aber je nach Schule zwischen 0% und 100%. Hohe Prävalenzraten wurden vor allem in der Tonkpi Region beobachtet. Zusammengenommen hatten 157 (59.5%) Schulen eine Prävalenz von mehr als 24%, 78 (29.5%) Schulen hatten eine Prävalenz zwischen 10% und 24%, und die verbleibenden 29 Schulen (11.0%) hatten eine Prävalenz unter 10%.

Mit Hilfe von Bayesischer Geostatistischer Analyse konnte gezeigt werden, dass Alter, Geschlecht, Höhe und unterschiedliche Landoberflächentemperaturen zu Tag und Nachtzeiten signifikant mit *S. mansoni* Infektionen korrelierten. Potentielle Risikofaktoren, die mit einer *S. mansoni* Infektion in den lokalen Gemeinschaften assoziiert waren, waren Reisanbau, offene Defäkation, die Benutzung von traditionellen Plumpsklos und die Nutzung von natürlichen offenen Süßgewässern zum Waschen und Baden.

Bei der Erhebung der Ausgangsdaten fanden wir in 28 (37.3%) von den 75 Schulen, deren *S. mansoni* Prävalenz bei der Eignungsstudie als moderat eingeschätzt worden war (10-24%), eine Prävalenz von mehr als 24%, wenn mindestens vier Kato-Katz Ausstriche pro Kind in Betracht gezogen wurden. In 7 Schulen (9.3%) war die Prävalenz unter 10%.

In Bezug auf die Behandlungsarme fanden wir, dass die *S. mansoni* Prävalenz in Arm C geringfügig höher als in Arm A oder B war. Unsere Daten zeigten, dass die Behandlung, die direkt beobachtet wurde, 84.2% der Kinder erreichte. Auf Schulebene wurde in 57 Schulen (76.0%) eine Behandlungsrate von mehr als 75% erreicht. Ein Jahr nach der Behandlung hatte sich die *S. mansoni* Prävalenz in den Behandlungsarmen A und B von 19.7% auf 12.8% verringert. Die Intensität der Infektion hatte sich hingegen leicht von 94.9 Eiern pro Gramm Stuhl auf 109.3 Eier pro Gramm Stuhl erhöht. Die Dynamik der *S. mansoni* Prävalenz und Intensität war heterogen.

Schlussfolgerung: Genauere Informationen über die räumliche Verteilung der Bilharziose können Entscheidungsträgern dabei helfen Interventionen zur Kontrolle der Erkrankung

besser zu planen. Im Rahmen dieser Doktorarbeit wurde eine räumlich explizite Risikokarte für *S. mansoni* im westlichen Teil der Elfenbeinküste erstellt, die bereits von dem Nationalen Kontrollprogramm benutzt wurde, um die Kontrollinterventionen gebietsweise zu planen. Zusätzlich zeigte die Studie, dass die Einordnung von Gemeinschaften basierend auf den Bilharziose Endemizitätskategorien gemäß der WHO Leitlinien anfällig ist und dass ein genaueres Mittel für die Einordnung von Gemeinschaften nötig ist. Die Erfassung der Ausgangsdaten der parasitologischen und sozioökonomischen Lage in den Dörfern lieferte wichtige Informationen für die vierjährige cluster-randomisierte Interventionsstudie die von SCORE finanziert wird, und welche dazu beitragen wird die besten Strategien zur nachhaltigen Kontrolle der intestinalen Bilharziose zu entwickeln.

Unsere Ergebnisse zeigten, dass die Dynamik der Bilharziose in den Studiengebieten ein Jahr nach der Behandlung heterogen war. Demzufolge besteht einerseits eine Notwendigkeit einer regelmäßigen Erfassung der Dynamik der Bilharziose während dieser SCORE Studie um unser Verständnis der Übertragungsdynamik zu vertiefen, andererseits könnte es sein, dass zusätzliche ganzheitlichere Kontrollinterventionen nötig sind, um die Erfolge der präventiven Massenbehandlung nachhaltig zu machen und um von der Morbiditätsreduzierung zur Elimination voranzuschreiten.

Résumé

Introduction: La chimiothérapie préventive est une stratégie de délivrance de médicaments antihelminthiques aux populations à risque de schistosomiase sans diagnostic préalable. Actuellement, l'Organisation Mondiale de la Santé (OMS) recommande cette stratégie de lutte contre la morbidité en ciblant six helminthiases majeures parmi les 17 maladies tropicales négligées (MTN) qui posent un considérable problème de santé publique and freinent le développement économique des pays tropicaux et subtropicaux. Parmi ces helminthiases, la schistosomiase affecte plus de 250 millions de personnes, principalement en Afrique sub-saharienne. Depuis le milieu des années 1980, la chimiothérapie préventive au praziquantel a été préconisée par l'OMS pour la lutte contre la schistosomiase. Un taux de couverture élevé de la chimiothérapie préventive dans les zones d'endémie prévient non seulement la morbidité et les séquelles à long terme de la schistosomiase, mais pourrait également interrompre la transmission de la maladie. L'objectif actuel de l'OMS pour le contrôle de la morbidité due à la schistosomiase est d'atteindre régulièrement au moins 75% et jusqu'à 100% des enfants d'âge scolaire dans les zones endémiques. Cet objectif ambitieux était soutenu par les donateurs internationaux et les compagnies pharmaceutiques qui ont décidé d'offrir gratuitement des comprimés de praziquantel aux pays endémiques. Pendant que la chimiothérapie préventive au praziquantel est employé à grande échelle, il y a plusieurs préoccupations, tels que l'échec du traitement à éliminer l'infection, le développement et la propagation de la résistance au médicament, le faible taux de couverture du médicament notamment après plusieurs années de traitement de masse, le manque de données de base pour une meilleure évaluation de l'impact du traitement et la durabilité de cette stratégie.

Objectifs: L'objectif général de cette thèse de doctorat Ph.D. était d'approfondir notre compréhension de l'épidémiologie et de la distribution spatiale de la schistosomiase mansoni dans quatre régions de l'ouest de la Côte d'Ivoire, et d'évaluer l'impact de la chimiothérapie préventive au praziquantel sur la schistosomiase un an après le traitement. L'étude a été réalisée dans le cadre d'une enquête multi-pays financée par le Consortium schistosomiase de recherche opérationnelle et d'évaluation (SCORE). Cette thèse avait quatre objectifs spécifiques. Tout d'abord, de contribuer à la conception d'un protocole d'étude dans le but de maintenir le contrôle de *S. mansoni* dans les zones d'endémicité modérée (prévalence de l'infection de référence: 10-24%). Deuxièmement, pour cartographier et prévoir la répartition spatiale de *S. mansoni* dans la partie ouest de la Côte d'Ivoire. Troisièmement, de déterminer la situation parasitologique et socio-écologique de base des communautés locales avant la

mise en œuvre d'un essai contrôlé randomisé pour le contrôle durable de la schistosomiase mansoni. Quatrièmement, pour évaluer l'impact de la chimiothérapie préventive au praziquantel sur la prévalence et l'intensité de *S. mansoni* et à déterminer la dynamique de l'infection, un an après le traitement.

Méthodes: Le travail sur le terrain pour ce Ph.D. a été subdivisé en trois parties: les enquêtes d'éligibilité, de base et de suivi un an post-traitement. L'enquête d'éligibilité a eu lieu de Juin à Août 2011 et en Décembre 2011. Des enquêtes parasitologiques transversales en milieu scolaire ont été menées dans les régions de Cavally, Guemon, Tonkpi, et Haut-Sassandra à l'ouest de la Côte d'Ivoire. Environ 50 enfants âgés de 13-14 ans par école ont été examinés pour la présence de l'infection à *S. mansoni* en utilisant la méthode Kato-Katz. Deux lames de Kato-Katz ont été préparées par échantillon de selles. 75 écoles avec prévalence de *S. mansoni* comprise entre 10% et 24% ont été sélectionnées pour une enquête de base plus détaillée et randomisées dans l'un des trois bras de traitement (A, B et C). Les enquêtes de base ont été réalisées entre Décembre 2011 et Février 2012. Environ 100 enfants âgés de 9-12 ans par école ont fourni trois échantillons de selles sur trois jours consécutifs, alors qu'un seul échantillon de selles a été collecté chez 100 élèves de première année. Les échantillons de selles ont été soumis à la méthode de Kato-Katz (double lames de Kato-Katz par échantillon de selles) pour l'identification et le dénombrement des œufs de *S. mansoni*. En outre, un questionnaire sur les facteurs socio-démographiques et écologiques susceptibles d'influencer la transmission de *S. mansoni* a été livré aux directeurs d'école et les chefs de village. En Juin 2012, un traitement de masse à base scolaire et communautaire au praziquantel (dose unique de 40 mg / kg) a été mené, ciblant les enfants d'âge scolaire vivant dans les zones avoisinantes des écoles. Le traitement au praziquantel a été administré aux enfants par des enseignants formés. En Mai 2013, un an post-traitement, une enquête a été menée dans les 50 écoles du bras de traitement A et B. Environ 100 enfants âgés de 9- 12 ans par école ont été examinés sur trois jours consécutifs pour la présence de l'infection à *S. mansoni* en utilisant la méthode de Kato-Katz. La prévalence et l'intensité de l'infection à *S. mansoni* ont été comparées entre les enquêtes de base et de suivi un an post-traitement dans les écoles respectives.

Résultats: A l'enquête d'éligibilité, 264 écoles ont été sélectionnées. La prévalence globale de *S. mansoni* était de 39,9%, variant de 0% à 100% à l'échelle des écoles. Les taux élevés de prévalence de *S. mansoni* ont surtout été observés dans la région de Tonkpi. Dans

l'ensemble, 157 (59,5%) écoles avaient une prévalence de *S. mansoni* au-dessus de 24%, 78 (29,5%) écoles avaient une prévalence comprise entre 10% et 24%, tandis que les 29 écoles restantes (11,0%) avaient des prévalences en dessous de 10%. L'analyse géostatistique Bayésienne a montré que l'âge, le sexe, l'altitude et la différence entre la température de surface la journée et la nuit étaient significativement corrélées avec l'infection à *S. mansoni*. La culture du riz, défécation en plein air, l'utilisation des latrines traditionnelles, l'utilisation des eaux douces naturelles ouvertes pour le lavage et le bain ont été des facteurs de risque potentiels associés à *S. mansoni* dans les communautés locales. A l'enquête de base, après avoir examiné au moins quadruple lames de Kato-Katz par enfant, parmi les 75 écoles où la prévalence de *S. mansoni* était modérée pendant l'enquête d'éligibilité (10-24%), nous avons trouvé que la prévalence de l'infection était plus de 24% dans 28 écoles (37,3%), alors qu'elle était en dessous de 10% dans 7 écoles (9,3%). Au niveau des bras de traitement, nous avons trouvé que la prévalence de *S. mansoni* du bras de traitement C était légèrement supérieure par rapport aux bras A et B. Nos données ont montré que le taux de couverture du traitement directement observé était de 84,2%. A l'échelle des écoles, nous avons trouvé que le taux de couverture $\geq 75\%$ était atteint dans 57 écoles (76,0%). Un an après traitement, la prévalence globale de *S. mansoni* dans les 50 écoles de bras de traitement A et B a diminué de 19,7% à 12,8%, tandis que l'intensité de l'infection a légèrement augmenté de 94,9 œufs par gramme de selles chez les enfants infectés à 109,3 œufs par gramme de selles. La dynamique de la prévalence et l'intensité de *S. mansoni* étaient hétérogènes.

Conclusion: La compréhension de la répartition spatiale de la schistosomiase peut aider les décideurs à une meilleure planification de la lutte contre la maladie. Dans le cadre de cette thèse, une cartographie spatiale explicite des risques de *S. mansoni* a été générée pour la partie ouest de la Côte d'Ivoire et a déjà été utilisée par le programme national de lutte pour le ciblage spatial des interventions de lutte. En outre, l'étude a montré que la classification des communautés selon les critères de l'OMS est fragile ce qui appelle à un outil plus précis de catégorisation des communautés sur la base de l'endémicité de la schistosomiase. La situation parasitologique et socio-écologique de base dans les villages ont fourni des informations importantes pour l'essai d'intervention randomisé en grappes de 4 ans financé par SCORE, pourra aider à déterminer les meilleures stratégies pour contrôler durablement la schistosomiase mansoni.

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1. Introduction

1.1. Schistosomiasis

1.1.1. Biology and life cycle

Schistosomiasis is a water-associated parasitic disease, caused by blood flukes of the genus *Schistosoma*. Six out of the 19 species of schistosomes infecting mammals are recognised pathogenic for humans: *Schistosoma guineensis*, *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni* and *S. mekongi* (WHO, 1993; WHO, 2013a; WHO, 2015). *S. haematobium* provokes urogenital schistosomiasis, while the other schistosome species cause intestinal schistosomiasis (Chen and Mott, 1989; Ross et al., 2002; Gryseels et al., 2006; WHO, 2013a; Colley et al., 2014).

The life cycle of *Schistosoma* spp is complex comprising five different morphologic forms: eggs, miracidia, sporocysts, cercariae and adult worms (Figure 1.1). Adult schistosomes are small haematophagous worms with a length ranging from 7 mm to 28 mm and a width from 0.3 mm to 0.6 mm, depending on species and sex (Krauss et al., 2003). Sexual dimorphism in schistosomes is marked: the male is larger than the female (average length: 12 mm, average width: 1.0 mm versus length: 16 mm, width: 0.5 mm). The body of the male worm is folded upon its ventral side forming a groove called the gynaecophoric canal where the slender female develop and maintain its reproductive activity.

Worm couples of the species *S. mansoni* live within the mesenteric veins and *S. haematobium* worm pairs inhabit the terminal venules in the wall of the bladder, the genitourinary system and the pelvic plexus within the distribution of the inferior vena cava of the definitive human host (Davis, 1996). The average life span of *S. mansoni* ranges between 3 and 10 years, but can be as long as 40 years (Warren et al., 1974; Chabasse et al., 1985). *S. haematobium* can live up to 3.4 years (Wilkins et al., 1984).

Adulte female *S. mansoni* worms lay around 200-300 eggs per day, while *S. haematobium* and *S. japonicum* can produce up to 300 and 3,000 eggs per day, respectively (Grevelding, 2004; Larry et al., 2005). Approximately, half of the eggs are trapped in the tissues and cause the inflammations that give rise to morbidity. The remaining eggs are shed into the environment through urine (*S. haematobium*) or faeces (other species) and can stay viable at least 7 days (Gryseels et al., 2006).

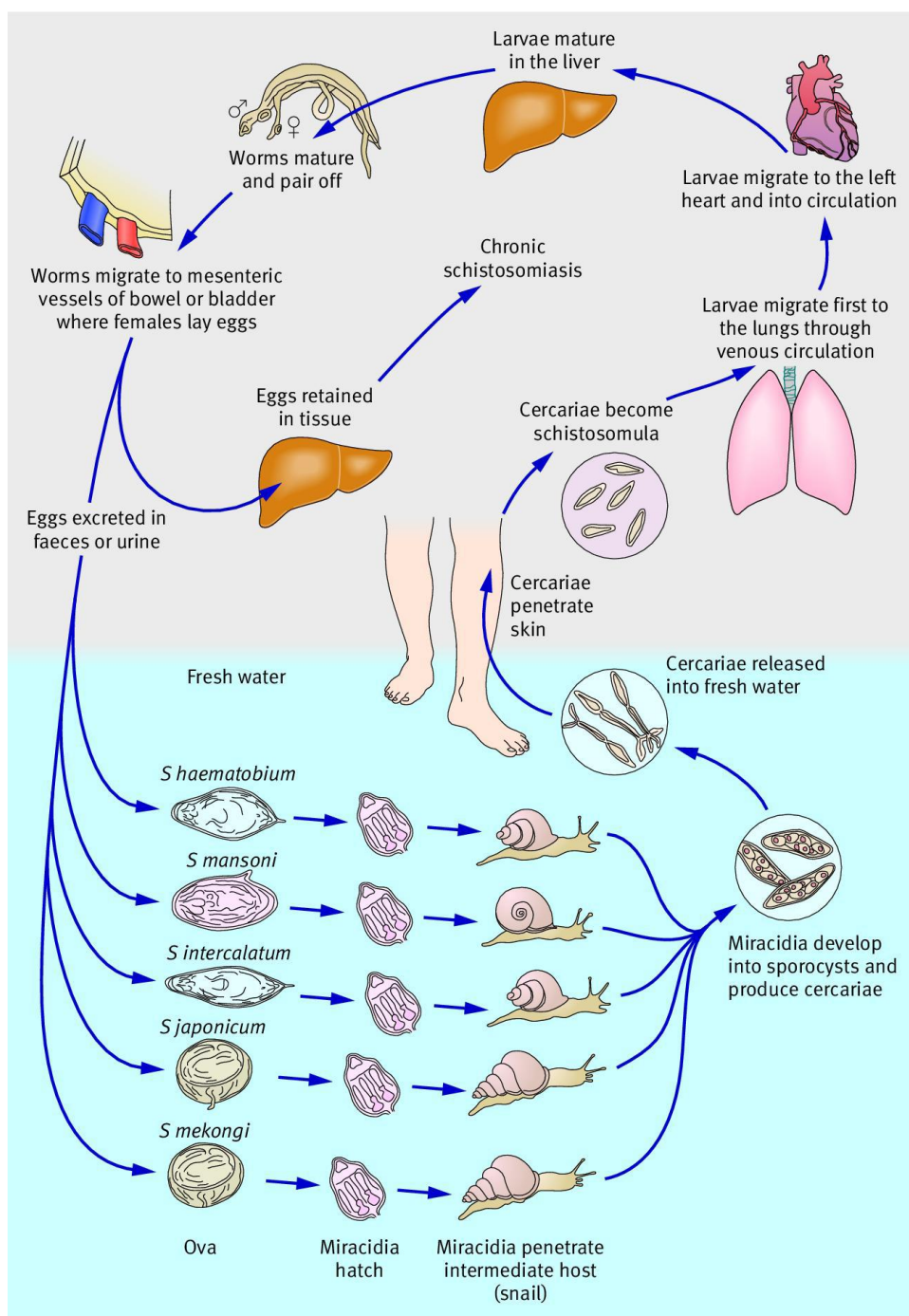


Figure 1.1: Life cycle of *Schistosoma* spp. (Gray *et al.*, 2011)

In a suitable freshwater bodies, the egg releases ciliated miracidia with 150 μm length which can penetrate into specific intermediate host snails (Beltran *et al.*, 2008). *S. mansoni* penetrates into the aquatic snails of genus *Biomphalaria*; *S. haematobium*, *S. intercalatum* and *S. guineensis* infect snails of the genus *Bulinus*; *S. mekongi* is transmitted by *Neotricula aperta* and *S. japonicum* infects amphibious snails of the genus *Oncomelania* (Gryseels *et al.*,

2006; Attwood and Upatham, 2013; Rollinson *et al.*, 2013). An egg produces approximately 250 to 600 miracidia (*S. mansoni*) and slightly (200) in case of *S. haematobium* (Ayad, 1974). Once a miracidium has penetrated into the snail, it multiplies asexually into sporocysts and then into cercariae. Cercariae measure about 450 µm in length (Beltran *et al.*, 2008). After 4-6 weeks the snail infection, cercariae are released into the freshwater (Gryseels *et al.*, 2006). If cercariae penetrate actively into the skin of humans (the definitive host) they migrate successively to the lungs and the liver, and transform into schistosomulae. In the portal vein, the schistosomulae mature into adult worms, which migrate to the vesical plexus (*S. haematobium*) or mesenteric venule (other species) mate, produce eggs and the life cycle continues.

1.1.2. Global burden of human schistosomiasis

Schistosomiasis is a complex of acute, but mainly chronic disease (Davis, 1996). Schistosomiasis negatively impacts the social and economic development of endemic countries. It has been estimated that approximately 800 million people in the world are at risk of schistosomiasis and more than 250 million people are infected (Steinmann *et al.*, 2006; Colley *et al.*, 2014; Hotez *et al.*, 2014). The burden of schistosomiasis is essentially concentrated in Africa; indeed, 90% of the infections and 85% of the people at risk live in Africa (Xue *et al.*, 2011; WHO, 2013b). In sub-Saharan Africa, the burden of schistosomiasis is estimated at 2.79 million disability-adjusted life years (DALYs) (IHME, 2013).

In 2010, it was estimated that the burden of schistosomiasis in Côte d'Ivoire was 69,700 DALYs (IHME, 2013). The estimated prevalence of *Schistosoma* spp infection among school-aged children in Côte d'Ivoire was 17.4% (Lai *et al.*, 2015).

1.1.3. Epidemiology

Figure 1.2 displays the distribution of schistosomiasis worldwide (Gryseels *et al.*, 2006). *S. japonicum* is endemic in the people's Republic of China, the Philippines and Indonesia; *S. mansoni* is found in Africa, the Arabian Peninsula and South America; *S. haematobium* occurs in Africa and the Arabian Peninsula. *S. intercalatum* is endemic in Central and Western Africa, while *S. guineensis* shows a more restricted geographical distribution and occurs in Cameroon, Gabon, Equatorial Guinea, Nigeria and São Tomé and Príncipe. *S. mekongi* is found only on Khong Island in Lao People's Democratic Republic and in Cambodia (Utzinger and Keiser, 2004; Muth *et al.*, 2010; Rollinson *et al.*, 2013). Recent

investigations showed that *S. haematobium* is endemic in Europe, particularly in Mediterranean areas (de Laval et al., 2014; Holtfreter et al., 2014; Boissier et al., 2015).

With regard to schistosomiasis in Côte d’Ivoire, the two species *S. mansoni* and *S. haematobium* overlap in the central and southern parts of the country (N’Guessan et al., 2007; Chammartin et al., 2013). *S. mansoni* is predominantly found in western Côte d’Ivoire while *S. haematobium* is mostly reported in the central part of the Côte d’Ivoire (N’Goran et al., 1998; Utzinger et al., 2000; Raso et al., 2005; N’Guessan et al., 2007; Coulibaly et al., 2012). An important feature of schistosomiasis is its focal distribution, which is the result of a combination of several factors: lack of access to sanitation and clean water, occurrence of suitable freshwater habitats for the intermediate host snails and human water contact activities (Lengeler et al., 2002; Beck-Worner et al., 2007; Krauth et al., 2015). Spatial heterogeneity of schistosome infections has been observed at district, country and regional levels (Raso et al., 2005; Schur et al., 2011; Chammartin et al., 2013). As it has been observed for other helminths of humans, aggregated distributions of the infection intensities have also been reported for schistosomiasis (Anderson and May, 1991).

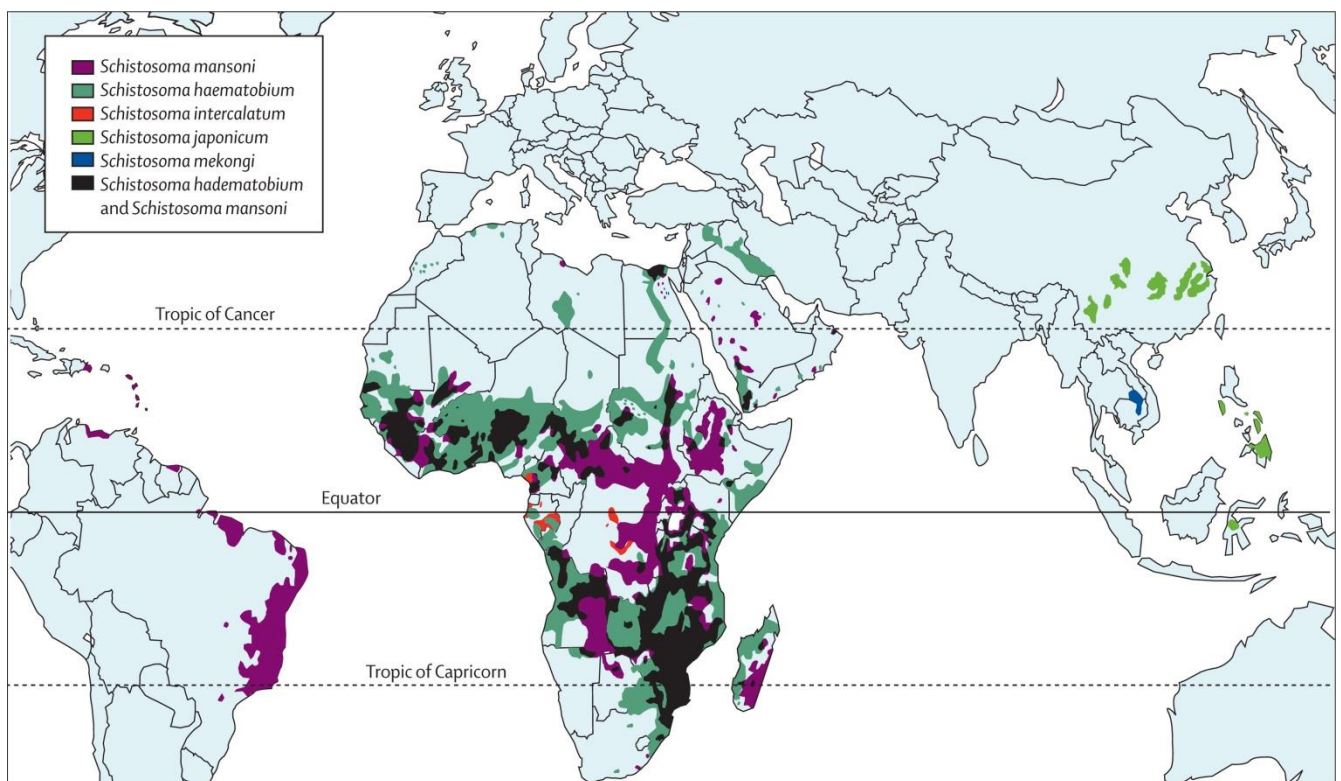


Figure 1.2: Global distribution of schistosomiasis (Ferrari and Moreira, 2011)

1.1.4. Pathology

Schistosome morbidity is largely due to the eggs retained in the tissues during the perivesical or peri-intestinal migration or after embolisation in the liver, spleen, lungs or cerebrospinal system. Those eggs secrete a proteolytic enzyme that lead to the infected immune responses and then the disease manifestations. In sub-Saharan Africa, it was estimated that more than half of the estimated 180 million schistosome-infected individuals suffer considerable associated morbidity, 18 million have bladder wall pathology, 10 million have hydronephrosis and 8.5 million have hepatomegaly (van der Werf et al., 2003).

Urogenital schistosomiasis due to *S. haematobium* can affect the urinary tract, resulting in haematuria, strictures, obstruction, super-infection and, ultimately, cancer (Salem et al., 2011). Intestinal schistosomiasis due to *S. mansoni* can cause several symptoms, including blood in the stool, abdominal pain, bloody diarrhoea, hepatomegaly, splenomegaly and marked eosinophilia (Lambertucci et al., 2000). Systemic effects such as anaemia, malnutrition, stunted growth and impaired cognition can be profound in children with heavy schistosome infections (Salem et al., 2011). Pulmonary schistosomiasis due to eggs of *S. haematobium* and *S. mansoni* can lead to glomerulonephritis (Schwartz et al., 2000; Barsoum, 2004). Genital schistosomiasis is due to eggs of *S. haematobium* and *S. mansoni* in the reproductive organs. In females, the symptoms include hypertrophic and ulcerative lesions of the vulva, vagina and cervix, which might facilitate sexual transmission of infections. The disease can lead to infertility. In men, the epididymis, testicles, spermatic chord and prostate can be affected; haemospermia is a common symptom (Gryseels et al., 2006). Neuroschistosomiasis is defined as the symptomatic or asymptomatic involvements of the central nervous system (CNS) by schistosomes. Infection of the spinal venous is due to eggs of *S. mansoni* and *S. haematobium*, while cerebral disease is associated with eggs of *S. japonicum* (Ferrari, 2004). The association of intestinal schistosomiasis and typhoid fever, hepatitis, pancreatitis, milliary tuberculosis, myelitis and appendicitis have also been reported (Neves et al., 1993; Knopp et al., 2013).

1.1.5. Diagnosis and treatment

Direct detection of schistosome eggs in the urine (i.e. *S. haematobium*) and stool samples all other schistosome species under a microscope is the most widely used diagnostic approach in epidemiological surveys. A commonly employed direct method for the diagnosis of urogenital schistosomiasis is the standard urine filtration method that involves the detection and

quantification of *S. haematobium* eggs in a 10 ml filtrate of a urine specimen that should be collected between 10:00 and 14:00 hours corresponding to the diurnal peak egg output (Plouvier et al., 1975; Mott et al., 1982). This method has high specificity and sensitivity (Plouvier et al., 1975). Quantification of faecal egg counts with the Kato-Katz method is the most widely used technique in epidemiological surveys pertaining to intestinal schistosomiasis and also other helminth infections (Katz et al., 1972; Booth et al., 2003). This technique is relatively simple and requires minimal equipment, but laboratory technicians have to be well-trained. Kato-Katz thick smears are usually prepared using 41.7 mg plastic templates (Speich et al., 2010; Yap et al., 2012). However, in area where infection intensities are low, this method presents some limitations as limited stool sampling may miss light infections due to poor sensitivity and day-to-day fluctuation in egg excretion (Barreto et al., 1990; Engels et al., 1996). Multiple stool sampling, with at least duplicate Kato-Katz thick smears per sample, is warranted to achieve a reasonable sensitivity (Utzing et al., 2011; Utzing et al., 2015).

Other parasitological, immunological, molecular and metabolic methods, such as Mini-FLOTAC, point-of-care circulating cathodic antigen (POC-CCA) urine assay, polymerase chain reaction (PCR) are specific and more sensitive (Utzing et al., 2011; Weerakoon et al., 2015). However, these methods require expensive laboratory infrastructure and highly accurate handling of samples, kits and equipment. Hence, such methods are often out of reach in resource-constrained settings.

1.2. Spatial distribution

1.2.1. Mapping tools: geographical information systems and remote sensing

A key epidemiological feature of schistosomiasis is its focal distribution resulting from many transmission factors. The common factors influencing schistosomiasis distribution are climate, vegetation and geographical location. Human exposure to contaminated water is influenced by the lack of sanitation, proper hygiene behaviours, irrigation and health system-related factors. Environmental transformations such as dam constructions and water management activities have been shown to play an important role in transmission (Steinmann et al., 2006). Therefore, development of models for predicting the spatial distribution of

schistosomiasis, taking into account the wealth of risk factors, is crucial for efficient control of the disease.

Remote sensing, in the broadest sense, refers to the acquisition of information of an object or phenomenon, employing a sensing device that is not in physical or intimate contact with the object itself. Remote sensing consists of the use of imaging sensor technologies aboard satellites primarily for the acquisition of environmental data. In 1984, remote sensing applications have been employed for the first time to predict the occurrence of human schistosomiasis in the Caribbean and the Philippines (Cross et al., 1984; Cross and Bailey, 1984). Geographical information systems (GIS) has been defined as “an organized collection of computer hardware, software, geographical data, and personnel designed to efficiently capture, store, update, manipulate, analyse, and display all forms of geographically referenced information” (ESRI, 1990). For disease epidemiology at an exploratory level, GIS is well suited for the study of associations between location, disease, vector/intermediate host and environment, due to its display capabilities. In 1994, remote sensing data coupled with a GIS were used to predict human schistosomiasis in the Nile delta area (Malone et al., 1994). Subsequently, numerous schistosomiasis studies combining remote sensing and GIS with spatial statistics have shown the importance of these tools in schistosomiasis control (Malone, 2005; Yang et al., 2005; Brooker, 2007). In western Côte d’Ivoire, a study has identified risk factors explaining the geographical distribution of *S. mansoni* infections in 57 randomly selected villages in the Man region and made predictions at non-sampled locations, using an integrated risk profiling approach consisting of remote sensing, GIS and Bayesian models (Raso et al., 2005). However, since the distribution of *S. mansoni* is focal, it is still necessary to extend such a study to the entire western part of Côte d’Ivoire in order to implement an effective control programme.

1.2.2. Risk factors

Anthropogenic factors

Human intrinsic factors such as genetics and immunity play a key role in the distribution of schistosomiasis. Several epidemiological observations suggest that the intensities of *S. mansoni* infection depend on host genetic factors, which could lead to susceptibility or resistance to infection (Katz et al., 1978; Butterworth et al., 1985; Dessein et al., 1988). It has been noted that immunity to *S. mansoni* develops progressively during childhood, peaking

around the age of puberty (Abel *et al.*, 1991). Demographic features, including sex, ethnicity and socio-economic status, also showed a strong influence on the geographical variation of *S. mansoni* (Raso *et al.*, 2005; Pinot de Moira *et al.*, 2010). Tourism, irrigated agriculture and dam construction further contribute to the dissemination of *S. mansoni* because these activities create favourable conditions for the intermediate host snails and facilitate the introduction of the schistosome to new areas (Poda *et al.*, 2004; Steinmann *et al.*, 2006; Enk *et al.*, 2010). It was estimated that 106 million people at risk of schistosomiasis lived in irrigation schemes or in close proximity to large dam reservoirs (Steinmann *et al.*, 2006).

Climatic factors

Rainfall is a key climatic factor that governs favourable conditions in numerous breeding sites for the intermediate host snails, and hence rainfall patterns, snail population density and schistosome transmission are associated (Xue *et al.*, 2011). Intermediate host snails for human schistosomes are unable to tolerate water flows of approximately 0.3 m/s, and above, and hence, intense rainfall and flooding reduce the number of snails found at potential transmission sites (Woolhouse and Chandiwana, 1990). On the other hand, intense rainfall and flooding could also be responsible for the re-introduction of snails and schistosomes to areas from which they had previously been eliminated and facilitate the spread of infected snails to areas that are newly suitable for snail populations and/or schistosome development (Walz *et al.*, 2015; McCrees and Booth, 2013). Therefore, rainfall accounts for a substantial part of the geographical variation in the prevalence of *S. mansoni* infection (Raso *et al.*, 2005).

The influence of temperature of water bodies on the development rate of the parasites within snails, the infectivity of cercariae and snail distribution is well known. The temperature is an important determinant of the limits of snail distribution and population size because egg production, hatching, juvenile maturation and death rates, and adult death rates are all affected by temperature (El-Hassan, 1974; Walz *et al.*, 2015). The rate of cercarial maturation inside infected snails increases as temperature increases (Foster, 1964). It is estimated that the optimum temperature for the development of *S. mansoni* is 20-27°C (Malone, 2005).

Environmental factors

Numerous studies on environmental features such as altitude, vegetation and distance from freshwater bodies have been used for mapping and prediction of schistosomiasis distribution.

Altitude is usually negatively correlated with the prevalence of schistosome infection. A previous study reported that children living in western Côte d'Ivoire at locations below 400 m were at a 5-fold higher risk of a *S. mansoni* infection when compared to those living at altitudes above this threshold (Raso *et al.*, 2005). The altitudinal threshold limit for *S. mansoni* transmission varies according to study area. It is less than 1,600 m in western Uganda, while an annual incidence of 0.20 infections per person at risk has been found at altitudes of 1,800-2,200 m in northern Ethiopia (Ghebreyesus *et al.*, 2002; Rubaihayo *et al.*, 2008). Water plants provide snails with shelter from the sun, egg-laying sites and a source of food. Thus, aquatic vegetation influences the distribution of snails across the globe (Brown, 1994; Pointier *et al.*, 2005). Several studies supported the use of vegetation for assessment of the distribution of schistosomiasis (Bavia *et al.*, 2001; Kristensen *et al.*, 2001). Distance from water body is usually negatively associated with *S. mansoni* prevalence (Handzel *et al.*, 2003; Odiere *et al.*, 2012). However, it was reported that there was no significant association between distance to permanent water bodies and *S. mansoni* infections in western Côte d'Ivoire (Raso *et al.*, 2005).

1.3. Prevention and control

1.3.1. Water, sanitation and hygiene (WASH)

In many part of the world, people do not have access to clean water, adequate sanitation facilities and good hygiene. In 2015, an estimated 663 million people still used unprotected wells, springs and surface water, half of them live in sub-Saharan Africa (UNICEF and WHO, 2015). Around 2.4 billion people worldwide still use inappropriate sanitation structures and more than 690 million of them living in sub-Saharan Africa (UNICEF and WHO, 2015). Recent observations revealed that inadequate WASH are common in large part of low- and middle-income countries and overlapped with schistosomiasis distribution (Campbell *et al.*, 2014). Numerous epidemiological studies demonstrated that the implementation of adequate WASH could reduce the prevalence and intensity of schistosome infections and other intestinal helminthic infections (Jordan *et al.*, 1978; Esrey *et al.*, 1991; Wang *et al.*, 2009; Grimes *et al.*, 2014). Therefore, in mid- 2012 the World Health Assembly (WHA) recommended on integrated control strategy that emphasis WASH alongside preventive chemotherapy. In schistosomiasis control, the role of safe water supply, adequate sanitation and good hygiene are to reduce water contact, prevent the contamination of freshwater with

excreta, to reduce the infectivity of cercariae and miracidia (Grimes et al., 2015). However, the success of the WASH interventions is associated to the setting characteristics such as the environmental factors such as the location of freshwater bodies and the presence of intermediate host snails, social and cultural factors that influence water-contact patterns and contamination behaviour (Grimes et al., 2015). Failure of these interventions to reduce schistosomiasis to low endemicity settings has been reported (Freeman et al., 2013; Knopp et al., 2013). In addition, the implementation of WASH is expensive and there are several challenges such as lack of health professional involvement, lack of local government involvement and local public-private partnerships for sanitation facilities construction, insufficient financial investment from governments and international foundations (OECD, 2000; Cairncross, 2003; Bartram and Cairncross, 2010).

1.3.2. Information, education and communication (IEC)

According to WHO, health education is an aspect of health care directed towards promoting and reinforcing healthy behaviour through full participation of the individuals and communities concerned (WHO, 1990). Since the 1930s, health education has been an integral part of schistosomiasis control program (Warren and Newill, 1967). The main purpose of IEC is to change the population behaviour in order to limit water contact, thus to reduce the risk of schistosomiasis transmission (Stothard et al., 2006; Stothard et al., 2009; Knopp et al., 2012). The intervention requires the involvement of people at all the levels of the community. Therefore, during the implementation of IEC, in addition to the education system, various communication tools must be considered, such as television and radio spots (mass media), road shows, public criers, leaflets, posters, comic strips, among others (Gabielli et al., 2006; Garba et al., 2006; Omedo et al., 2014). The key messages about the transmission of schistosomiasis and how the disease can be prevented have to be tailored to specific settings and translated and communicated in different languages. This strategy leads to widen the knowledge of the population about the transmission of schistosomiasis and how the disease can be prevent and controlled.

Several epidemiological research studies and national schistosomiasis control programme demonstrated that IEC could be used to lower the prevalence and intensity of *Schistosoma* infection (Santana et al., 1997; Chen et al., 2009). The important strength of the IEC is the ability to prevent the schistosomiasis but also to increase compliance with regard to other control tools (Utzinger et al., 2005). Previous studies underscored the relevance of

community participation in schistosomiasis control (Tanner et al., 1986; Guo et al., 2005). Recent studies revealed that IEC increased the awareness and compliance of other schistosomiasis control interventions (Zhou et al., 2013; Omedo et al., 2014). Therefore, IEC is a useful tool, which can be readily integrated with other control strategies, such as the preventive chemotherapy to control and ultimately eliminate schistosomiasis. Although IEC is a relevant aspect of schistosomiasis control; it has a limited impact on schistosomiasis in short term (Schall, 1995; Stothard et al., 2006; Rollinson et al., 2013). Therefore behaviour change by IEC requires long-term commitment (Stothard et al., 2006; Kojima et al., 2007).

1.3.3. Snail control

Reducing the intermediate host snail population by applying molluscicide, competitor snails, predator fish, prawns and environmental management is an important component of schistosomiasis control programmes. Niclosamide is the only chemical molluscicide recommended by WHO as it has high efficacy, low toxicity and causes comparatively little environmental contamination. During the 1950s and 1960s, large-scale schistosomiasis control programmes have been implemented in Sudan and Egypt with the use of molluscicides (Sharaf and Nagar, 1955; Chu, 1976). Despite its track record to have a significant impact on the transmission dynamics of schistosomiasis by killing snails, molluscicides are rarely used in contemporary schistosomiasis control programmes because such a control strategy remains expensive and unsustainable (Fenwick and Savioli, 2011; Knopp et al., 2012).

1.3.4. Chemotherapy

Drugs

Chemotherapy for human schistosomiasis consists of antischistosomal drugs for prevention of morbidity in high-risk populations and treatment of patients by eliminating adult worms, whose eggs, when deposited in human tissue, cause pathogenesis (Liu *et al.*, 2011). At present, chemotherapy is the main measure employed for the control of schistosomiasis in endemic countries (WHO, 2002; WHO., 2012). Praziquantel remains the only drug currently recommended by WHO for individual treatment and community-based morbidity control for all types of schistosomiasis (WHO, 2013b). At the individual patient level, praziquantel is usually administered at a single oral dose of 40 mg/kg of body weight (WHO, 1995). For

preventive chemotherapy, praziquantel is often administered based on a dose pole, which allows drug administration based on people's height rather their weight (Montresor *et al.*, 2002). Praziquantel is efficacious against adult schistosome species that infect humans (Liu *et al.*, 2011). This drug is safe and often provided for free of charge to national control programmes. The main limitation of praziquantel is the lack of therapeutic efficacy against young developing schistosomes, which might explain local treatment failure in highly endemic areas and observed high rates of re-infection post-treatment (Del Villar *et al.*, 2012). Moreover, praziquantel remains the only drug recommended by the WHO for the treatment of all forms of schistosomiasis, and hence, it has become the drug of choice in both clinical practice and public health interventions (WHO, 2013b).

Oxamniquine, a drug that exhibits activity against *S. mansoni* is more effective against male parasites (Ferrari *et al.*, 2003). Its immediate toxicity is low and presents weak side effects. Many studies have reported the failures of oxamniquine treatment that could explain the decline of its use (Conceição *et al.*, 2000; Clarke *et al.*, 1976).

Metrifonate (10 mg/kg) administered three times with four months intervals showed similar benefit compared to one dose of praziquantel (40 mg/kg) in reducing prevalence and intensity of *S. haematobium* and associated morbidity (King *et al.*, 1990). Despite, the efficacy of metrifonate against *S. haematobium*, this drug has recently been withdrawn from the market because of medical, operational and economic drug criteria (Cioli, 2000).

Artemether and artesunate and other artemisinin derivatives with anti-schistosomal potential are active against *S. japonicum*, *S. mansoni* and *S. haematobium*, mainly targeting the immature, stage (Xiao and Catto, 1989). Although a series of randomised controlled trials have shown potential of the artemisinins to fight schistosomiasis (Utzinger and Keiser, 2004), they are not being recommended against schistosomiasis, perhaps because of the fear of malaria resistance development.

Preventive chemotherapy

Since the mid-1980s, WHO emphasises morbidity control using praziquantel as the main pillar of the global strategy to control schistosomiasis (WHO., 1985). The cornerstone of this recommendation is the repeated large-scale administration of anthelmintic drugs to at-risk populations (WHO., 2006). The population at risk is usually categorised according to school-aged children (5-14 years of age) and adults (≥ 15 years) in the general population. The

frequency of preventive chemotherapy depends on the population risk category (Table 1) (WHO, 2002).

According to data published by WHO, more than 39 million Africans were treated for schistosomiasis in 2013 (WHO, 2015). However, this represents only 12.7% of the individuals requiring preventive chemotherapy. Therefore, much effort is still needed in order to achieve recommended coverage levels of at least 75 % among school-aged children (WHO, 2002; WHO, 2006).

1.4. Identified research needs

The upscale of schistosomiasis control in the next years will not only need highly dedicated development partners, governments, health workers, drug distributors and local communities, but will also involve major costs. To assess which strategy for mass drug administration (MDA) of praziquantel provides the best balance in terms of cost and reductions in prevalence and intensity of *S. mansoni* and/or *S. haematobium* in school-aged children, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE), in collaboration with African, American and European partners, designed a series of multi-year cluster-randomised trials that are being implemented since 2010 in Côte d'Ivoire, Kenya, Mozambique, Niger and the United Republic of Tanzania (Figure 1.3).

Two of the studies are evaluating alternative approaches to MDA in communities with high prevalence rates (>25% in school-aged children) of either *S. mansoni* or *S. haematobium* and are termed “Gaining control of schistosomiasis” studies. These studies are conducted in Kenya, Mozambique, Niger and the United Republic of Tanzania. The remaining two studies are evaluating alternative approaches to MDA in areas of moderate prevalence (10-24% in school-aged children) of either *S. mansoni* or *S. haematobium* and are entitled “Sustaining control of schistosomiasis” studies. The latter studies are conducted in Côte d'Ivoire and Kenya.

The current Ph.D. thesis is embedded in the SCORE project which is taking place in western Côte d'Ivoire. This work consists of a rigorous evaluation of alternative strategies of MDA with praziquantel in areas where the prevalence of *S. mansoni* is moderate.

Table 1.1: Recommended treatment strategies against schistosomiasis, as recommended by WHO.

Community category	Prevalence in school survey	Intervention in schools enrolled and non-enrolled children	Health services and community-based intervention
I High prevalence	≥30% visible haematuria (<i>S. haematobium</i> , by questionnaire) or ≥50% infected (<i>S. mansoni</i> , by parasitological method)	Targeted treatment of school-aged children, once a year	Access to praziquantel for passive case treatment; community-directed treatment for high-risk groups recommended
II Moderate prevalence	<30% (<i>S. haematobium</i> by questionnaire) or ≥10% but <50% infected (<i>S. mansoni</i> and <i>S. haematobium</i> , by parasitological methods)	Targeted treatment of school-aged children, once every 2 years	Access to praziquantel for passive case treatment
III Low prevalence	<10% infected (<i>S. mansoni</i> and <i>S. haematobium</i> , by parasitological methods)	Targeted treatment of school-aged children twice during primary schooling (once on entry, again on leaving)	Access to praziquantel for passive case treatment

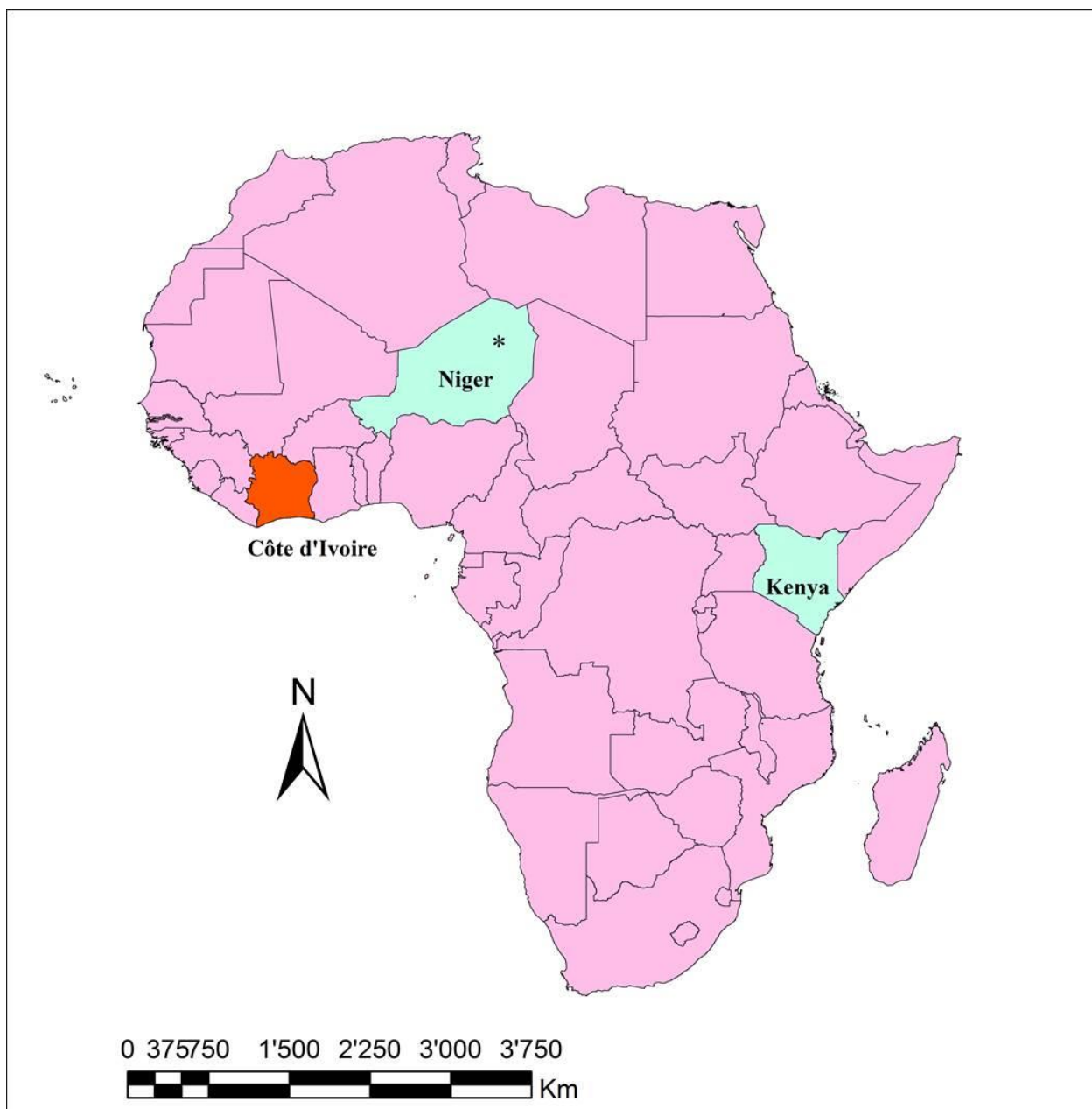


Figure 1.3: African countries where “Gaining and sustaining schistosomiasis control” studies are currently being implemented.

*After 2 years, Niger has been subjected to another control programme.

1.5. Goal and specific objectives

1.5.1. Goal

The overarching goal of this Ph.D. project is to implement and adhere to a SCORE study protocol for sustaining the control of schistosomiasis mansoni in the western part of Côte d'Ivoire.

1.5.2. Specific objectives

- * To contribute to the development and implementation of a study protocol that will be implemented to control *S. mansoni* in an area with moderate endemicity.
- * To map and predict the spatial distribution of *S. mansoni* in the western part of Côte d'Ivoire.
- * To determine the baseline characteristic of local communities before the implementation of a cluster-randomised controlled trial to sustain schistosomiasis mansoni control.
- * To assess the impact of preventive chemotherapy with praziquantel on the prevalence and intensity of *S. mansoni* and the dynamic of the infection one year after the intervention.

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2. Paper 1 - Sustaining control of schistosomiasis mansoni in moderate endemicity areas in western Côte d'Ivoire: a SCORE study protocol

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2.1. Abstract

Background: Schistosomiasis is a parasitic disease that occurs in the tropics and subtropics. The mainstay of control is preventive chemotherapy with praziquantel. In Africa, an estimated 230 million people require preventive chemotherapy. In western Côte d'Ivoire, infections with *Schistosoma mansoni* are widespread. To provide an evidence-base for programme decisions about preventive chemotherapy to sustain control of schistosomiasis, a 5-year multi-country study with different treatment arms has been designed by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) and is currently being implemented in various African settings, including Côte d'Ivoire.

Methods/Design: We report the study protocol, including ethics statement and insight from a large-scale eligibility survey carried out in four provinces in western Côte d'Ivoire. The study protocol has been approved by the ethics committees of Basel and Côte d'Ivoire. A total of 12,110 children, aged 13–14 years, from 264 villages were screened for *S. mansoni* using duplicate Kato-Katz thick smears from single stool samples. Among the schools with a *S. mansoni* prevalence of 10–24%, 75 schools were selected and randomly assigned to one of three treatment arms. In each school, three stool samples are being collected from 100 children aged 9–12 years annually and one stool sample from 100 first-year students at baseline and in the final year and subjected to duplicate Kato-Katz thick smears. Cost and coverage data for the different intervention arms, along with environmental, political and other characteristics that might impact on the infection prevalence and intensity will be recorded in each study year, using a pretested village inventory form.

Discussion: The study will document changes in *S. mansoni* infection prevalence and intensity according to different treatment schemes. Moreover, factors that determine the effectiveness of preventive chemotherapy will be identified. These factors will help to develop reasonable measures of force of transmission that can be used to make decisions about the most cost-effective means of lowering prevalence, intensity and transmission in a given setting. The gathered information and results will inform how to effectively sustain control of schistosomiasis at a low level in different social-ecological contexts.

Trial registration: ISRCTN99401114 (date assigned: 12 November 2014).

Keywords: Schistosomiasis, *Schistosoma mansoni*, Control, Morbidity control, Preventive chemotherapy, Praziquantel, Prevalence, Intensity of infection, Côte d'Ivoire, SCORE

2.2. Background

2.2.1. Burden and transmission of schistosomiasis, with an emphasis on *Schistosoma mansoni* in Africa

Human schistosomiasis, a disease caused by chronic infection with parasitic trematodes of the genus *Schistosoma*, is endemic in 78 tropical and subtropical countries, 42 of which are located in Africa (WHO, 2014). An estimated 779 million people are at risk of schistosomiasis, more than 230 million are infected, 120 million are symptomatic and 20 million suffer from severe and debilitating forms of schistosomiasis (Chitsulo et al., 2000; Steinmann et al., 2006; Vos et al., 2012; Colley et al., 2014). The burden of the disease is essentially concentrated in Africa, where more than 90% of the infections worldwide occur (Utzinger et al., 2009; WHO, 2013; Colley et al., 2014). Schistosomiasis is intimately connected with poverty, and hence, the disease delays the social and economic development in endemic countries (Gryseels et al., 2006; King, 2010; Utzinger et al., 2011; Colley et al., 2014).

The life cycle of schistosomiasis involves a phase of sexual reproduction by adult schistosome worms in the definitive human host, and an asexual phase in the intermediate host, a specific freshwater snail. In Côte d'Ivoire, for example, *Biomphalaria pfeifferi* is the only intermediate host snail for *Schistosoma mansoni* (N'Goran et al., 1989). From the snail, cercariae are released into the surrounding water and can invade humans through the skin. Infection with *S. mansoni* causes intestinal schistosomiasis. Typical symptoms include blood in the stool, (bloody) diarrhoea, chronic or intermittent abdominal pain, anaemia, general fatigue, weight loss, hepatomegaly, splenomegaly and marked eosinophilia (Lambertucci et al., 2000; Gryseels et al., 2006). Moreover, chronic infection can impair children's physical and cognitive development and nutritional status (King et al., 2005). Associations of intestinal schistosomiasis with hepatitis, acquired immunodeficiency syndrome (AIDS) and malaria hypertension have been reported (Al-Shamiri et al., 2011; Mazigo et al., 2013; Kinung'hi et al., 2014).

Several factors contribute to the spread of schistosomiasis. Demographic features, including age, gender, ethnicity and socioeconomic status have a strong influence on the spatial distribution of schistosomiasis, particularly *S. mansoni* (Raso et al., 2005; Pinot de Moira et al., 2010). Tourism, construction and operation of water resource developments (i.e. irrigation schemes and dams) are associated with higher risks of *S. mansoni*, explained by the creation of favorable conditions for intermediate host snails and higher frequencies of human

water contacts (Poda et al., 2004; Enk et al., 2010; Colley et al., 2014). It is estimated that more than 100 million people at risk of schistosomiasis live in irrigation schemes or in close proximity to reservoirs of large dams (Colley et al., 2014). Intense rainfall and flooding might be responsible for the reintroduction of intermediate host snails to areas from which schistosomiasis had previously been eliminated (McCreesh and Booth, 2013).

2.2.2. *Schistosomiasis control in Africa*

According to the World Health Organization (WHO), comprehensive schistosomiasis control programmes should include treatment of at-risk groups, provision of clean water, adequate sanitation, hygiene education and snail control (WHO, 2002). The current mainstay of control is preventive chemotherapy – that is the periodic administration of the antischistosomal drug praziquantel to entire at risk populations without prior diagnosis. The goal is to cover at least 75% of those at risk of schistosomiasis by preventive chemotherapy in 2020 (WHO, 2013). The frequency of preventive chemotherapy is guided by infection prevalence in specific age groups. In areas where the prevalence of *Schistosoma* infection in school-aged children (5–14 years) is 50% or higher, entire communities should be treated once every year; if the prevalence is between 10% and 50%, treatment is focussed on school-aged children with a frequency once every two years; if the prevalence is below 10%, school-aged children should be treated twice, at school entry and again before they finish schooling (WHO, 2002; WHO., 2012b). In Africa, approximately 35.5 million people were treated with praziquantel in 2012 (WHO, 2014). This estimate accounts for a coverage of only 13.6% of schoolaged children. Hence, concerted efforts are needed to massively scale-up preventive chemotherapy to reach the 75% coverage goal by the year 2020. In Côte d’Ivoire, where both *S. mansoni* and *S. haematobium* are endemic and many people suffer from intestinal or urogenital schistosomiasis (Doumenge et al., 1987; N’Goran et al., 1998; Utzinger et al., 2000c; Raso et al., 2005; N’Guessan et al., 2007; Tchuem Tchuente and N’Goran, 2009; Chammartin et al., 2013), no large-scale preventive chemotherapy programme was in place prior to the onset of this study in 2011 (Utzinger et al., 2000a; Raso et al., 2004; Tchuem Tchuente and N’Goran, 2009).

2.2.3. *Operational research for schistosomiasis control*

Further up-scaling of schistosomiasis control in the years to come will not only need political commitment, national strategic plans, dedicated development partners, functioning health systems and community volunteers, but will also involve major costs. To assess which

strategy of preventive chemotherapy will provide the best balance in terms of reduction in prevalence and intensity of schistosome infection in school-aged children on one hand, and costs on the other hand, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE; <http://score.uga.edu/>) designed a series of largescale, multi-country intervention studies. In response to a request for proposals to gain and sustain control of schistosomiasis in Africa, several investigators from Africa, in partnership with colleagues from Europe and the United States of America, put forward their ideas. The proposals were evaluated by a panel of experts against predefined criteria. Initially, three projects were selected under the heading “Sustaining control of schistosomiasis”, focusing either on *S. mansoni* (two projects; Côte d’Ivoire and Kenya) or *S. haematobium* (one project; Niger). The overarching goal is to evaluate alternative approaches to preventive chemotherapy in areas with moderate prevalence of infection at baseline (10-24% in school-aged children). Of note, the sustaining schistosomiasis haematobium project in Niger has been terminated after two years due to an issue with the randomisation of study villages.

Here, we summarise the relevant part of a harmonized study protocol that is being followed by partners conducting the sustaining control of schistosomiasis mansoni studies in Côte d’Ivoire and Kenya. The field and laboratory procedures for the sustaining *S. mansoni* control project in moderate endemicity areas of Côte d’Ivoire will be presented in greater detail, including results of the initial eligibility survey, which guided the selection of 75 communities or villages for subsequent treatment interventions.

2.2.4. Goal, aims and objectives

The goal of the SCORE projects aiming at sustaining control of schistosomiasis at a low level is to generate an evidence-base for programme decisions about preventive chemotherapy-based approaches to sustain the control of *S. mansoni* infections. The studies will determine which strategy for preventive chemotherapy provides the best balance in terms of cost and the reduction in prevalence and intensity of infection in school-aged children after four years of intervention. The studies are designed to answer the following question: How can we sustain control of *S. mansoni* in communities/villages with a moderate endemicity level (prevalence of 10-24%, as assessed by a single stool examination with duplicate Kato-Katz thick smears)? Specifically, we are addressing the following research questions:

- What combination of annual school-based treatment (SBT) and “drug holidays” yields the best outcomes for the lowest cost?
- What are the factors that determine the effectiveness of preventive chemotherapy?

- Can reasonable measures of force of transmission be developed that can be utilised to make decisions about the most cost-effective means of lowering prevalence, intensity and transmission in a given setting?

2.3. Methods/Design

2.3.1. Study design

The SCORE sustaining schistosomiasis control studies are designed as randomised intervention trials with three study arms. Each arm comprises 25 communities or villages. Hence, the studies will include 75 communities per country. Communities will be provided with various combinations of SBT and “drug holidays” over a 4-year period, followed by final data collection, analysis and dissemination of results in the fifth year. The intervention arms in the sustaining schistosomiasis control studies are designed as shown in Figure 2.1. In brief:

- schools of arm A will receive annual SBT for four years;
 - schools of arm B will receive SBT in the first two years, followed by “drug holidays”;
- and
- schools of arm C will receive SBT in years 1 and 3, alternated by “drug holidays” in years 2 and 4.

Preventive chemotherapy with praziquantel is being provided as single oral dose of 40 mg/kg, using a dose pole. Standard praziquantel treatment exclusion criteria apply (WHO, 2002). No treatment will be provided during “drug holidays” and no parasitological data are collected in those years. During SBT, praziquantel will be administered by trained teachers to all school-going children. Children in all schools in the community will be treated, and hence, children attending schools not otherwise involved in the study will also receive treatment. Any time SBT will take place, additional efforts will be made to enhance treatment coverage, such as community sensitization and mobilization efforts, radio announcements, and other means of information, education and communication (IEC) strategies. Non-school attendees who span the same age range as school-going children will also be invited for treatment. No other major treatment strategies outside the education sector venue will be implemented. The school attendance rates and treatment coverage will be documented throughout the study.

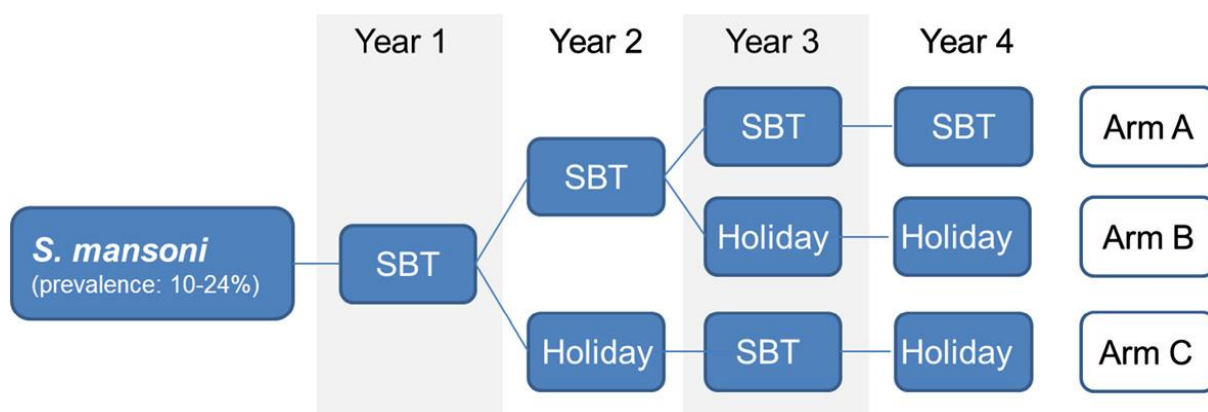


Figure 2.1: Study arms for the sustaining control of *Schistosoma mansoni* studies in moderate endemicity areas (prevalence: 10-24%).

SBT, school-based treatment; Holiday, no drug delivery.

2.3.2. Justification of the number of intervention arms and participants

The protocol for the sustaining schistosomiasis control studies was developed through a series of expert consultations, facilitated by the SCORE secretariat and its scientific advisory board. The decision to choose three intervention arms for the current studies took into consideration formal sample size calculation and operational feasibility. For sample size calculation, it was assumed that the treatment interventions will reduce *Schistosoma* prevalence in moderate endemicity areas from 25% to 10%. Analyses determined the minimum effect size that may be detected with 90% power for a 2-sided $\alpha = 0.05$ level test as a function of the number of children m tested per village, the number n of villages sampled per treatment, the overdispersion parameter ϕ , and the correlation ρ between observations in year 1 at baseline and in year 4 at the end of the study. The calculations revealed that studying 20 communities or schools per arm and evaluating 100 individuals per school would result in minimum effect sizes of 5-12% with or without overdispersion. This minimum effect size was deemed reasonable. To further increase the chance of detecting differences between the interventions arms, the number of the units of interventions, and hence, the number of schools, was increased to 25 per arm. Taken together, the trial protocol asked to examine 100 children aged 9–12 years every year whenever drug intervention will be implemented as primary outcome. Additionally, 100 first-year students will be examined in years 1 and 5.

2.3.3. *Eligibility of study communities*

Sustaining schistosomiasis control studies will include 75 communities with an initial *S. mansoni* prevalence of 10-24%. Selection of these large numbers of communities has been determined through a rapid appraisal eligibility survey. A single stool sample from each of 50 children aged 13–14 years has been subjected to duplicate Kato-Katz thick smears (Katz et al., 1972; Knopp et al., 2013). Additional criteria applied for eligibility determination are as follows. First, a study community must have a primary school, because the arms of the study are school-based and every participating community must be eligible to be randomised to any of the study arms. However, it is permitted that a study community may have more than one school. If two nearby communities have schools with less than 100 children per school but they are similar in terms of ecology and socioeconomic status, they can be combined for purposes of this study and be considered as a single study community. Second, two nearby communities that share water sources and/or whose schools have overlapping catchment areas will not be considered separate villages for the purposes of this study; one of the two schools will be chosen. Third, there is no pre-set population requirement for the size of a community, as long as it includes at least 100 children aged 9-12 years who attend school. Fourth, preference is for settings that have not recently been subjected to preventive chemotherapy targeting schistosomiasis. If communities have been previously treated, historic treatment data should be included where available. Fifth and finally, to the extent possible, study communities should be as similar as possible in characteristics that could affect transmission dynamics, including, for example, a history of past treatment and the availability of water sources.

2.3.4. *Eligibility of study participants*

For the eligibility study to rapidly identify the 75 communities with a baseline prevalence of 10-24%, children were eligible to participate if they were 13 or 14 years old and provided an informed consent sheet signed by their parents. In the baseline and the yearly follow-up surveys conducted to assess the change in prevalence and intensity of *Schistosoma* infection in each intervention arm, children aged 9–12 years who provide a written informed consent from their parents will be included. Additionally, in years 1 and 5, first-year students will provide written informed consent from their parents and will participate in the study.

2.3.5. Details of the *S. mansoni* control study in western Côte d'Ivoire

Study area and population

The sustaining *S. mansoni* control study in Côte d'Ivoire is being conducted by a team of researchers from the Université Félix Houphouët-Boigny, who work in close collaboration with the Programme National de Lutte contre la Schistosomiase, les Géohelminthiases et la Filariose Lymphatique (PNL-SGF) at the Ministry of Health and Public Hygiene, the 'Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS), all based in Abidjan, and the Swiss Tropical and Public Health Institute (Swiss TPH) in Basel, Switzerland.

The study area is located in western Côte d'Ivoire in the four regions Cavaly, Guemon, Haut-Sassandra and Tonkpi (Figure 2.2). The area was chosen because it is a well known *S. mansoni* focus (N'Goran et al., 1998) and our teams conducted schistosomiasis research there since the mid- 1990s, including treatment of individuals found positive upon Kato-Katz examination (Doumenge et al., 1987; Utzinger et al., 1998; Keiser et al., 2002; Raso et al., 2005; Beck-Worner et al., 2007; Matthys et al., 2007; Tchuem Tchuente & N'Goran, 2009; Chammartin et al., 2013). Cavaly, Guemon and Tonkpi regions are located west of the Sassandra River and belong to the district des Montagnes. Ten departments of this district are included in our study: Bangolo, Biankouma, Danané, Douékoué, Facobly, Guiglo, Kouibly, Man, Sipilou and Zoukougbeu. The district des Montagnes is a mountainous area with an average altitude ranging between 300 m and slightly above 1,000 m. The climate is humid tropical with two seasons. The rainy season usually lasts from March to October. The Haut-Sassandra region is located East of the Sassandra River. Zoukougbeu is the only department of that region which is included in our study. Here, the average altitude ranges between 200 m and 300 m. The climate is sub-equatorial, characterised by two rainy seasons. The long rainy season occurs from March to July and the short rainy season from September to October.

According to the national population census carried out in 1998 (the most recent census at the time of writing the current piece), the total population in the study area is 1.5 million people (unpublished data; Institut National de la Statistique en Côte d'Ivoire). Most people belong to one among the four ethnic groups: Bété, Guéré, Wobé and Yacouba. People are mainly engaged in subsistence farming (cassava, maize, plantain and rice). There is also production of cash crops (coffee and cocoa) and a small forestry industry in the town of Man (Utzinger et al., 2000b). The annual rainfall in the study area varies between 1,100 and 2,000 mm. The vegetation is composed of two types of forests (semi-deciduous and evergreen mountain forest). The average annual temperature is around 26°C.

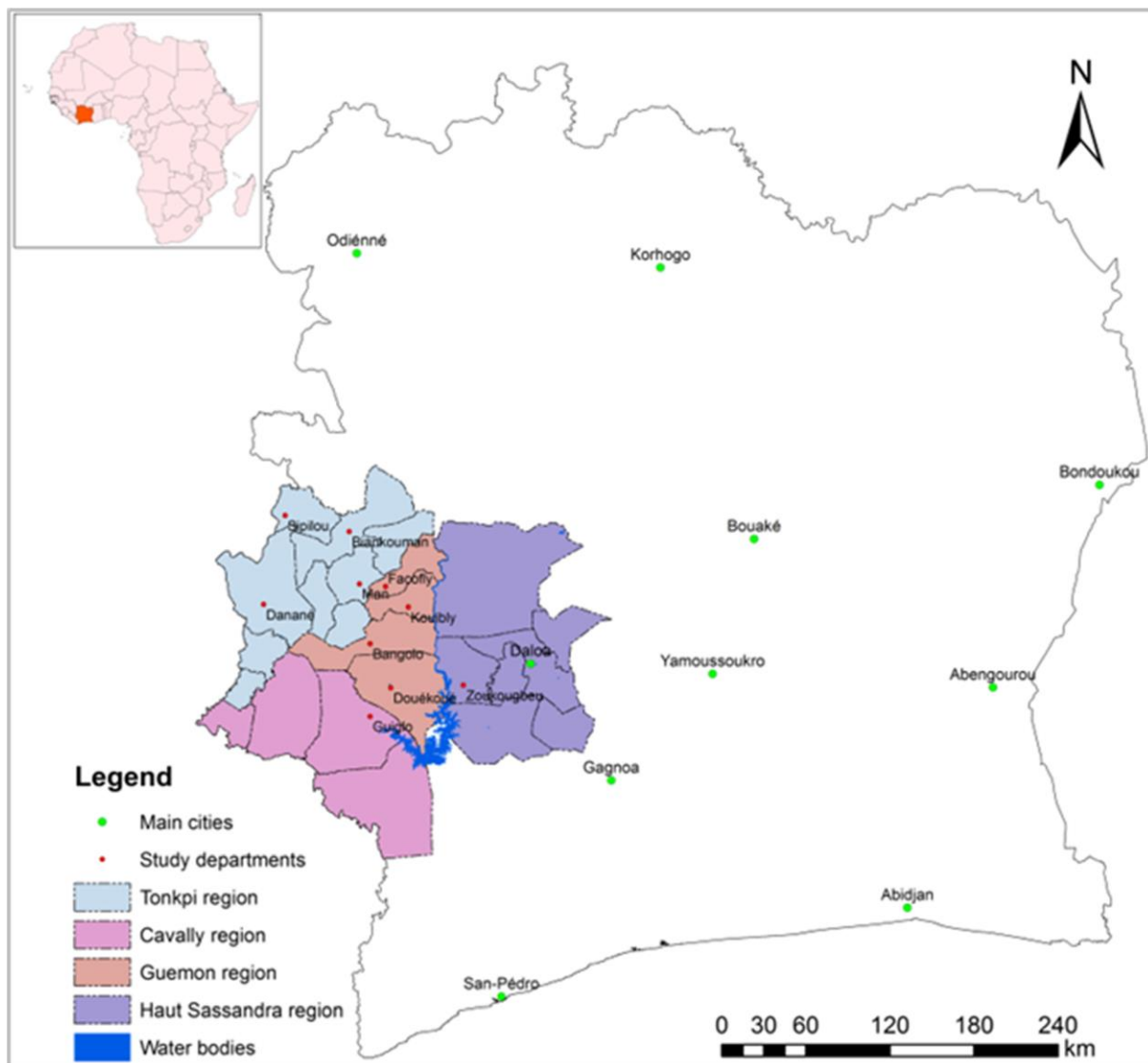


Figure 2.2: Map of Côte d’Ivoire with the four study regions in the western part where the SCORE sustaining *S. mansoni* control project is being implemented.

Selection and randomisation of study villages

The 75 villages with a *S. mansoni* prevalence of 10-24% in western Côte d’Ivoire were identified as follows. First, our team organised a series of meetings with health and education authorities in the four study regions. The purpose and procedures of the study were explained and a total of 264 communities fulfilling the following criteria were identified: (i) village has a school attended by at least 100 children aged 9–12 years in grades 2–5 and 50 children aged at least 13 years in grades 4–6; (ii) village and school had no recent history of preventive chemotherapy using praziquantel against schistosomiasis (within the past 12 months); (iii) village is accessible also in the rainy season; and (iv) it is safe for our teams to work in the village. The latter issue was a real concern, as Côte d’Ivoire suffered from a decade-long

political unrest that culminated in armed conflict and war in late 2010/early 2011 (Bonfoh *et al.*, 2011). Before the onset of the surveys in each school, we conducted a brief interview with the school teachers to assess the selectability of the villages, according to the aforementioned criteria. Then, schoolchildren in grades 1–6 were informed about the mode of transmission of *S. mansoni*, its health impact and the importance of the current project. Children aged 13 or 14 years were randomly selected from grades 4–5 until the number of children reached 50. In settings where less than 50 children aged 13–14 years were present, the sample was completed with 12-year-old children, but these children will not be enrolled in the subsequent randomised controlled trial.

Children were asked to provide a written informed consent from their parents or legal guardians. Children with written informed consent were supplied with plastic containers to collect a small amount of their own early morning stool specimen. Collection containers were labelled with unique identification numbers. The name, sex, age and school grade of each child were recorded. Stool samples were transferred to the Centre Hospitalier Regional de Man for parasitological examination. From each stool sample, duplicate Kato-Katz thick smears were prepared on microscope slides using 41.7 mg templates (Katz *et al.*, 1972; Knopp *et al.*, 2013). After allowing the slides to clear for at least 60 min, they were examined under a microscope by experienced laboratory technicians for the presence of *S. mansoni* and soil-transmitted helminths (i.e. *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*).

The prevalence of *S. mansoni* was calculated for each school. A total of 12,110 children submitted a stool sample that was subjected to duplicate Kato-Katz thick smears. The prevalence at the unit of the school in the eligibility survey ranged from 0% to 100% (Figure 2.3). In brief, among the 264 schools, 157 (59.5%) had a *S. mansoni* prevalence above 24%, 78 (29.5%) schools had a prevalence ranging between 10% and 24%, whilst the remaining 29 schools (11.0%) had a prevalence below 10%. As shown in Figure 2.4, most of the villages meeting the sustaining control prevalence range (i.e. 10-24%) that were ultimately selected (n = 75) are located in the Guemon region. The schools were randomly assigned to three intervention arms using a computer-based randomisation procedure conducted by an independent statistician.

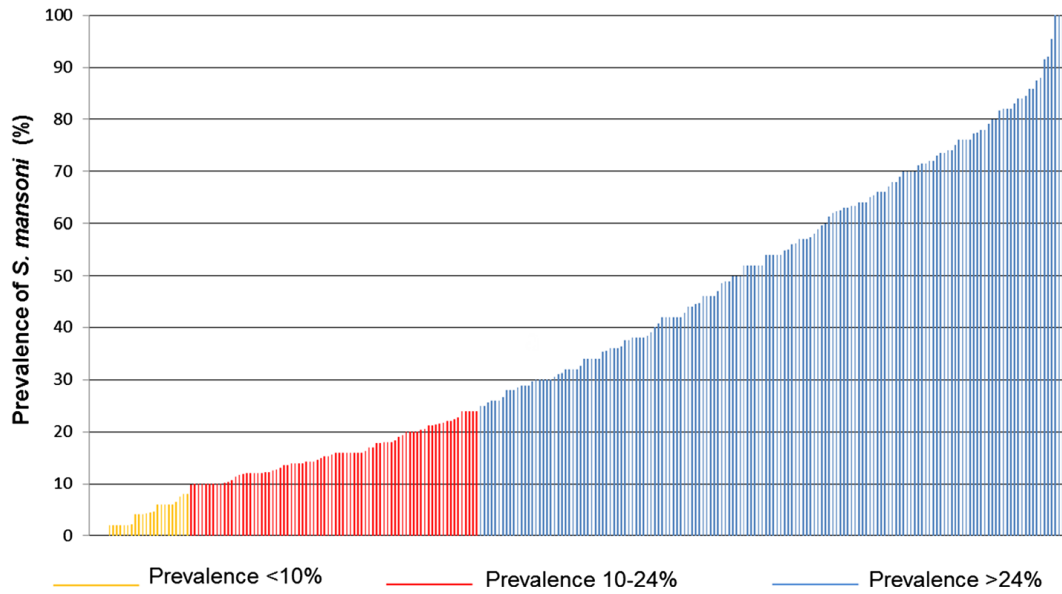


Figure 2.3: Range of prevalence of *S. mansoni* infection in the 264 villages screened in western Côte d’Ivoire to identify moderate *S. mansoni* endemicity areas (10-24%).

At the unit of the school, we examined 50 children aged 13–14 years with duplicate Kato-Katz thick smears from a single stool sample.

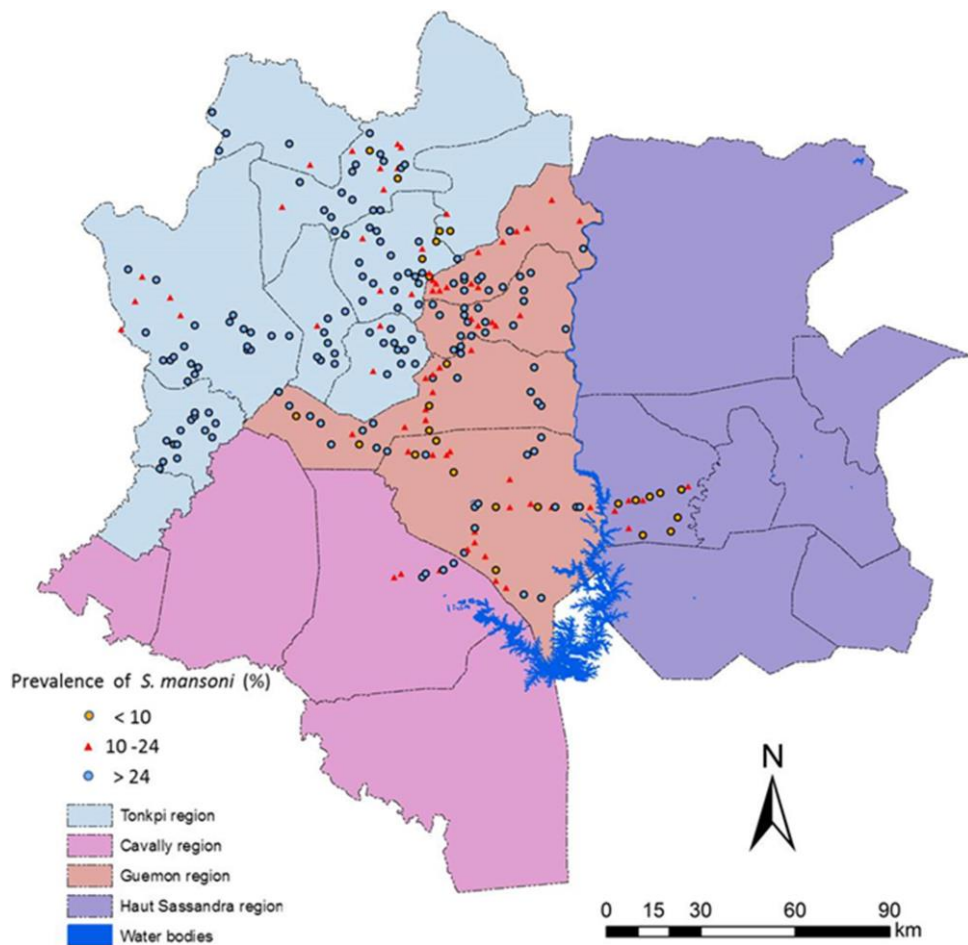


Figure 2.4: Map showing point prevalence of *S. mansoni* in 264 schools of western Côte d’Ivoire, as determined by an eligibility survey in late 2011/early 2012.

2.3.6. *Data collection in the main study*

Collection of stool samples and administration of a questionnaire

At the beginning of the main activities of the sustaining *S. mansoni* control study in the western part of Côte d'Ivoire, a small designated team informed district and village authorities and children's parents. Detailed information was provided about the forthcoming cross-sectional parasitological and questionnaire surveys. Each year, shortly before the annual parasitological survey, teachers will be re-informed about the purpose and procedures of the study. Teachers assist by preparing class lists, including name, age, sex and school grade. In each school, children aged 9–12 years are enrolled from grades 2–6 until 100 pupils will be reached. Moreover, at baseline and in the final year of the study, 100 pupils will be randomly selected from the class list of grade 1 and their age will be recorded. Before sample collection commences, the study is explained in lay terms to the selected children and they are invited to provide three stool samples over consecutive days. Stool samples are collected in 125 ml plastic containers.

Children are asked to return the containers within an hour, filled with an apricot-sized portion of their own stool. We collect the containers and label them with individual IDs. The stool collection procedure is repeated over three consecutive days. Children without written consent from their parents and those who are unable to produce at least two stool samples are withdrawn, but they receive praziquantel treatment as the other children in the same village. For final analysis those children who have written consent and results from at least four Kato-Katz thick smears are included.

Upon visiting the school by our team, the community leader is contacted and interviewed with a pre-tested questionnaire to record characteristics of demography, main activities, health system, water contact sites, and sources of water and sanitary facilities in the village. Demographic information includes the number of households and total population. The health system is characterized by accessibility to health infrastructures, and availability of praziquantel against schistosomiasis and artemisinin-based combination therapy (ACT) against malaria. Information pertaining to water contact sites comprises the number of stagnant and non-stagnant freshwater bodies. The questionnaire also allows determining which type of water the population uses for drinking, bathing and cleaning. We also assess which type of sanitary facilities the population uses (i.e. pit latrine, ventilated improved pit latrine, toilet or any other kind of facilities).

Overall, the plan is to collect 22,500 stool samples from children aged 9–12 years and 7,500 stool samples from first-grade children at baseline (year 1) and at the end of the study (year 5). In years 2, 3 and 4, a total of 15,000 stool samples will be collected from children aged 9–12 years. Children on “drug holidays” will not be subjected to stool examination.

Laboratory procedures to assess S. mansoni infection

Fresh stool samples are transferred to central laboratories at the hospitals of Bangolo, Biankouma, Danané, Douékoué, Guiglo, Kouibly and Man. The stool samples are subjected to the Kato-Katz method (Katz *et al.*, 1972; Knopp *et al.*, 2013). In brief, duplicate Kato-Katz thick smears are prepared from each sample using standard 41.7 mg templates. After a clearing time of at least 60 min, the thick smears will be examined under a microscope by experienced laboratory technicians. Eggs of *S. mansoni* and soil-transmitted helminths (*A. lumbricoides*, hookworm and *T. trichiura*) are counted and recorded for each species separately. For quality control, 10% of the slides are randomly selected and re-examined by a senior microscopist. The results are compared with the results of the first examination by the team. Slides identified with discrepant results (e.g. *S. mansoni* egg-positive vs. egg-negative or difference of *S. mansoni* egg counts of more than 20%) are reexamined until agreement has been reached. Given the large number of slides processed in the eligibility survey, parts of the slides were transferred to Abidjan and were examined microscopically within a maximum of 3 months after stool collection. All record sheets will be transferred to the Université Félix Houphouët-Boigny, where data entry, cleaning and database management take place.

SBT and assessment of coverage

District and community medical personnel are associated with the SBT in Côte d’Ivoire. Teachers and community health workers are trained to sensitize the communities, to administer drugs to the children and to monitor adverse events. Different sensitization tools are implemented such as radio and television announcements, along with other IEC strategies. During SBT, praziquantel is administered by trained teachers to all children attending school. Children in all schools in the community are treated, even if the school is not among the 75 schools where children are being tested. Efforts are made to reach out to non-enrolled children to enhance treatment coverage. Treatment is supervised by physicians and implemented by trained school teachers. Praziquantel tablets are delivered using a WHO dose pole (Montresor *et al.*, 2002). Children are monitored for adverse events for 4 hours after treatment and, if need be, appropriate medical action is taken. Treatment will be led by the PNL-SGF, and

supported by staff from the Programme National de Santé Scolaire et Universitaire (PNSSU). Financial support to facilitate treatment is provided by SCORE, while praziquantel tablets are supplied by the Schistosomiasis Control Initiative (SCI).

Data collection, management and statistical analysis

In the eligibility and baseline surveys, data are collected on paper form, but then, starting at year 2, smartphones have been utilised for data collection in the field and laboratory. Data cleaning and management is done by a designated database manager (PKY) at the Université Félix Houphouët-Boigny in Abidjan. Demographic and parasitological data directly entered in smartphones are uploaded to a database maintained on a central server (Open Data Kit) hosted by the SCORE secretariat at the Task Force for Global Health in Atlanta, United States of America. Data from questionnaire records will be entered in Microsoft Excel (2010 Microsoft Corporation). Statistical analyses will be carried out in STATA version 12 (StataCorp.; College Station, TX, USA). The primary outcome will be the change in prevalence and intensity of *S. mansoni* infection in the cohort of 9- to 12-yearold children over the four years of intervention. For each year, prevalence and infection intensity data will be calculated as described below. The results from the different study arms will be compared on an annual basis and at the end of the 4-year intervention period. Each child with at least one *S. mansoni* egg identified in at least one of the Kato-Katz thick smears will be considered as positive. Eggs per gram of stool (EPG) will be determined for each child by calculating the arithmetic mean *S. mansoni* egg counts from all Kato-Katz thick smear readings and by multiplication with a factor 24. The *S. mansoni* infection intensity will be categorised according to WHO guidelines into light infection (1–99 EPG), moderate infection (100–399 EPG) and heavy infection (≥ 400 EPG) (WHO, 2002).

School attendance rate will be documented throughout the study. The treatment coverage will be determined by (i) calculating the percentage of pupils treated among the total children registered in the school and (ii) calculating the percentage of school-aged children not attending school who are treated according to data from community health workers.

To guarantee the privacy of individuals, a separate and confidential file will be kept, detailing names against ID numbers. All data will be stored in purpose-built MS Excel files with no names but only ID numbers and will be kept by the data manager at the Université Félix Houphouët-Boigny. A safety copy will be stored in a secured locker. Only authorized persons will have access to the data within the context of the project, and the data will be backed-up regularly and safely. In addition, all work stations of data entry clerks will be

protected by case-sensitive passwords and there will be no sharing of any account or password information between staff and other individuals not concerned with the project. When discussing or showing the results of analyses in public venues, the information will always be reported at an aggregate level so that individual participants cannot be identified.

Protocol review and ethical clearance

The study protocol has been approved by the institutional research commissions of Swiss TPH in Basel and CSRS in Abidjan. Ethical approval was obtained from the ethics committees in Basel (reference no. EKBB 279/10; Basel, 21 October 2010) and Côte d'Ivoire (reference no. 1994 MSHP/CNER; Abidjan, 5 May 2010). The trial is registered at controlled-trials.com (identifier: ISRCTN99401114; date assigned: 12 November 2014). Informed consent is obtained from parents or legal guardians of all pupils involved in the study. Children are treated with praziquantel (40 mg/kg) using a dose pole (Montresor *et al.*, 2002) in the frame of SBT. Efforts will be made to reach out to non-enrolled children.

The results of this study may be published, but subjects' names or identities will not be revealed. Records will remain confidential and the results of tests will be codified to prevent association with participants' names. Data entered into computerized files will be accessible only by authorized personnel directly involved in the study. Subject-specific information will be provided to medical personnel only with the subject's permission.

2.4. Discussion

Human schistosomiasis is a chronic and debilitating disease responsible for an estimated global burden of 3.3 million disability-adjusted life years (Murray *et al.*, 2012). In Africa, 230 million people currently require preventive chemotherapy (Vos *et al.*, 2012). The goal set by the WHO for the year 2020 is to treat at least 75% of school-aged children at risk of schistosomiasis with praziquantel as the only drug (WHO, 2013). Various partners, institutions and pharmaceutical companies have agreed in the London Declaration of 2012 that they will contribute to achieving this goal with donation of praziquantel and other support to facilitate and sustain drug administration at large scale (WHO., 2012a). The SCORE study described here will provide an evidence base for programme decisions about the type and frequency of preventive chemotherapy that is required to sustain control of schistosomiasis *mansoni* in areas where the baseline prevalence of infection ranges between 10% and 24%. The study will show for well characterized settings across Africa which treatment scheme (yearly treatment of school-aged children, or treatment interspaced by holidays) will yield the

best result and at what cost. Moreover, factors that determine the effectiveness of large-scale deworming will be identified. These factors will help to develop measures of force of transmission that can be utilised to make decisions about the most cost-effective means of lowering the prevalence and intensity of *Schistosoma* infection and the force of the transmission in a given setting. The data generated might shape future treatment schedules to sustain the control of schistosomiasis at low level elsewhere in sub-Saharan Africa and perhaps in Asia and Latin America where schistosomiasis also remains endemic, in preparation for a move to eliminate this disease in suitable locations.

In western Côte d'Ivoire, infections with *S. mansoni* are common (Doumenge et al., 1987; Utzinger et al., 1998; Raso et al., 2005) but until the mid-1990s, the extent of endemicity was not well understood. Some control efforts had been implemented in the 2000s, but due to a decade-long socio-political crisis, control had been interrupted (Tchuem Tchuente & N'Goran, 2009; Bonfoh et al., 2011). The large eligibility study conducted to select 75 villages with a moderate *S. mansoni* prevalence (10-24%) clearly revealed that *S. mansoni* in the western part of Côte d'Ivoire is rampant; among 264 schools screened, 157 (59.5%) had a *S. mansoni* prevalence above 24%, while 78 schools (29.5%) were in the desired prevalence range of 10-24% and only 29 schools (11.0%) had a prevalence below 10%. The eligibility survey employed an insensitive diagnostic approach (i.e. duplicate Kato-Katz thick smears based on a single stool sample). Had more intensive sampling and a more sensitive diagnostic method been employed (e.g. three stool samples subjected to triplicate Kato-Katz per stool sample or a point-of-care circulating cathodic antigen (POC-CCA) urine cassette test), a much higher overall prevalence of *S. mansoni* would have been found (de Vlas & Gryseels, 1992; Utzinger et al., 2001; Booth et al., 2003; Enk et al., 2008; Colley et al., 2013). In order to respect World Health Assembly (WHA) resolution 54.19 endorsed in May 2001, which emphasizes preventive chemotherapy targeting school-aged children to control morbidity (WHO, 2001), and in view of a more ambitious WHA resolution 65.21 put forth in May 2012, the new declared goal is to move from morbidity control to elimination of schistosomiasis (Knopp et al., 2013; Rollinson et al., 2013). Hence, authorities of Côte d'Ivoire have established the PNL-SGF in June 2007 (Tchuem Tchuente & N'Goran, 2009). Hand-in-hand with the SCORE sustaining schistosomiasis control operational research study reported here, the national schistosomiasis control programme was reinforced, with additional support from SCI. This study will provide data that may be used by SCORE, SCI, WHO and other partners to deploy the best tools and strategies to control morbidity due to schistosomiasis, and thus contribute to the reduction of poverty in schistosomiasis-endemic countries.

2.5. Acknowledgments

We are grateful to the members of the SCORE secretariat and advisory committee for reviewing our study, their advice, input and support of our work. We are grateful to Dr. Jan Hattendorf and Ms. Yingsi Lai from the Swiss Tropical and Public Health Institute for the randomisation of the schools and help with the mapping, respectively. We thank the technicians from different institutions of Côte d'Ivoire for their support in the field and the laboratory, particularly Mr. Laurent K. Lohourignon and Mr. Raphael G. Diabré. We are grateful to the health, education and village authorities of the regions of Cavaly, Guemon, Haut-Sassandra and Tonkpi for their contribution. We acknowledge teachers, students and parents for their participation in the study. We thank the team of the Laboratoire de Zoologie et de Biologie Animale at the Université Félix Houphouët-Boigny for their support in the field and in the laboratory. We are grateful to Prof. Bassirou Bonfoh, Director-General of the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire for his support.

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3. .Paper 2 - The spatial distribution of *Schistosoma mansoni* in four regions of western Côte d'Ivoire

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3.1. Abstract

Schistosomiasis poses a considerable public health burden in sub-Saharan Africa and a sound understanding of the spatial distribution facilitates to better target control interventions. The objectives of this study were i) to assess the prevalence of *Schistosoma mansoni* among school-aged children in four regions of western Côte d'Ivoire; ii) to determine demographic, climatic and environmental factors that influence the distribution of *S. mansoni*; and iii) to map and predict the distribution of *S. mansoni* in non-sampled locations. Parasitological surveys were carried out in 264 schools from June to December 2011. In each school, we aimed to examine 50 children for *S. mansoni* infection using duplicate Kato-Katz thick smears. Schools were georeferenced using a hand-held global positioning system receiver. Demographic data were obtained from readily available school lists, while climatic and environmental data were extracted from open-access remote sensing databases. Multivariable, binary non-spatial models and a Bayesian geostatistical logistic regression model were used to identify demographic, climatic and environmental risk factors for *S. mansoni* infection. Risk maps were developed based on observed *S. mansoni* prevalences and using Bayesian geostatistical models to predict prevalences at non-sampled locations. Overall, 12,462 children provided a sufficiently large stool sample to perform at least one Kato-Katz thick smear. The observed overall prevalence of *S. mansoni* infection was 39.9%, ranging from 0 to 100% at the unit of the school. Bayesian geostatistical analysis revealed that age, sex, altitude and difference between land surface temperature at day and night were significantly associated with *S. mansoni* infection. The *S. mansoni* risk map presented here is being used by the national schistosomiasis control programme for spatial targeting of praziquantel and other interventions.

3.2. Introduction

Despite increasing efforts to control schistosomiasis, this chronic, parasitic disease still affects more than 250 million people and causes a global burden of 3.3 million disability-adjusted life years (DALYs) (Murray et al., 2012; Hotez et al., 2014). There are six *Schistosoma* species infecting humans and the most important ones are: *S. haematobium*, *S. japonicum* and *S. mansoni* (Gryseels et al., 2006; Colley et al., 2014). In sub-Saharan Africa, urogenital schistosomiasis (caused by *S. haematobium*) and intestinal schistosomiasis (caused by *S. mansoni*) inflict a considerable public health problem, particularly in poor rural communities (King, 2010; Utzinger et al., 2011).

The main measures for controlling schistosomiasis are i) preventive chemotherapy (i.e. large-scale distribution of the antischistosomal drug praziquantel to populations at risk of infection to prevent morbidity); ii) improvement of clean water supply and sanitation; iii) intermediate host snail control; and iv) information, education and communication (IEC) targeting high-risk populations to limit their infection exposure by behavior change (Engels et al., 2002; WHO, 2002; Utzinger et al., 2011; Knopp et al., 2013; Rollinson et al., 2013; Grimes et al., 2014). To adequately target preventive chemotherapy and other control measures against schistosomiasis, the endemicity levels need to be known. High-risk communities can be identified, for example, by screening urine or stool specimens of school-aged children for *Schistosoma* eggs, or by assessing self-reported blood in urine or stool, or self-reported exposure to natural open freshwater bodies using questionnaires (Lengeler et al., 2002a; WHO, 2002).

Numerous studies have demonstrated that geographical information system (GIS), remote sensing and geostatistical analysis are powerful approaches for disease risk profiling and risk mapping at large-scale (Brooker et al., 2003; Raso et al., 2006; Clements et al., 2009; Karagiannis-Voules et al., 2015). Particularly in developing countries, where resources for disease control are scarce, these means can assist health authorities in identifying high risk areas, including very remote settings, which are difficult to access, and in adequately targeting intervention measures for disease control (Stensgaard et al., 2005). In Côte d'Ivoire, these epidemiological and geostatistical tools were previously applied to study the impact of environmental change on the prevalence of Buruli ulcer (Brou et al., 2008) and to map and predict the spatial distribution of schistosomiasis in the mountainous region of Man (Raso et al., 2005) and across the country (Chammartin et al., 2014).

Schistosomiasis is characterised by a focal distribution, which is the result of a complex interplay of behavioural, climatic and environmental factors that influence the dynamics and density of intermediate host snails and the infection prevalence and intensity in humans. For example, distance from people's residency to open freshwater bodies is usually negatively associated with the prevalence of *S. haematobium* (Rudge et al., 2008) and *S. mansoni* (Handzel et al., 2003; Odiere et al., 2012). Altitude is also an important factor associated with the occurrence of schistosomiasis (Kabatereine et al., 2004; Raso et al., 2005). *Biomphalaria pfeifferi*, the intermediate host snail of *S. mansoni*, requires temperature values ranging between 15 and 31°C and pH values ranging from 6.8 to 8.6, to thrive successfully (Utzinger et al., 1997; McCreesh and Booth, 2014; Walz et al., 2015). *Bulinus globosus*, one of the intermediate host snails of *S. haematobium*, shows preferences for freshwater bodies

with temperatures ranging from 14 to 32°C and pH values from 6.0 to 7.8 (Woolhouse and Chandiwana, 1990; Yapi et al., 2014b; Walz et al., 2015). Hence, for schistosomiasis risk prediction, it is important that multiple environmental factors are considered.

The goal of the current study was to generate a risk map for *S. mansoni* in four regions of western Côte d'Ivoire that can help the national schistosomiasis control programme in decision making for adequately targeting preventive chemotherapy and other control interventions. The data were obtained from a large-scale eligibility survey conducted as part of a sustaining schistosomiasis control project requested by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) (Assaré et al., 2014). The risk maps already proved useful for the national schistosomiasis control programme in Côte d'Ivoire.

3.3. Materials and methods

3.3.1. Ethical considerations

The institutional research commissions of the Swiss Tropical and Public Health Institute (Basel, Switzerland) and the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (Abidjan, Côte d'Ivoire) approved the study protocol. Ethical clearance was provided by the ethics committees in Basel (reference no. EKBB 279/10) and the Ministry of Public Health in Côte d'Ivoire (reference no. 1994 MSHP/CNER).

Before launching any field activities, the region education directors, education inspectors and officers were informed about the objectives and procedures of the study. These authorities informed village leaders and teachers who then informed village committees and schoolchildren, respectively. At the day of the survey, teachers and schoolchildren were provided with additional information about the study purpose and field and laboratory procedures. Written informed consent was obtained from parents and legal guardians of children. Children found infected with *S. mansoni* were treated with praziquantel, administered at a single oral dose of 40 mg/kg of body weight (WHO, 2002).

3.3.2. Study area and population

The study was carried out in four regions of western Côte d'Ivoire: Cavally, Guemon, Tonkpi and Haut-Sassandra, extending from 6°28'47.5'' to 7°52'10.0'' N latitude and from 6°44'09.8'' to 8°21'30.0'' W longitude (Figure 3.1). The Cavally, Guemon and Tonkpi regions

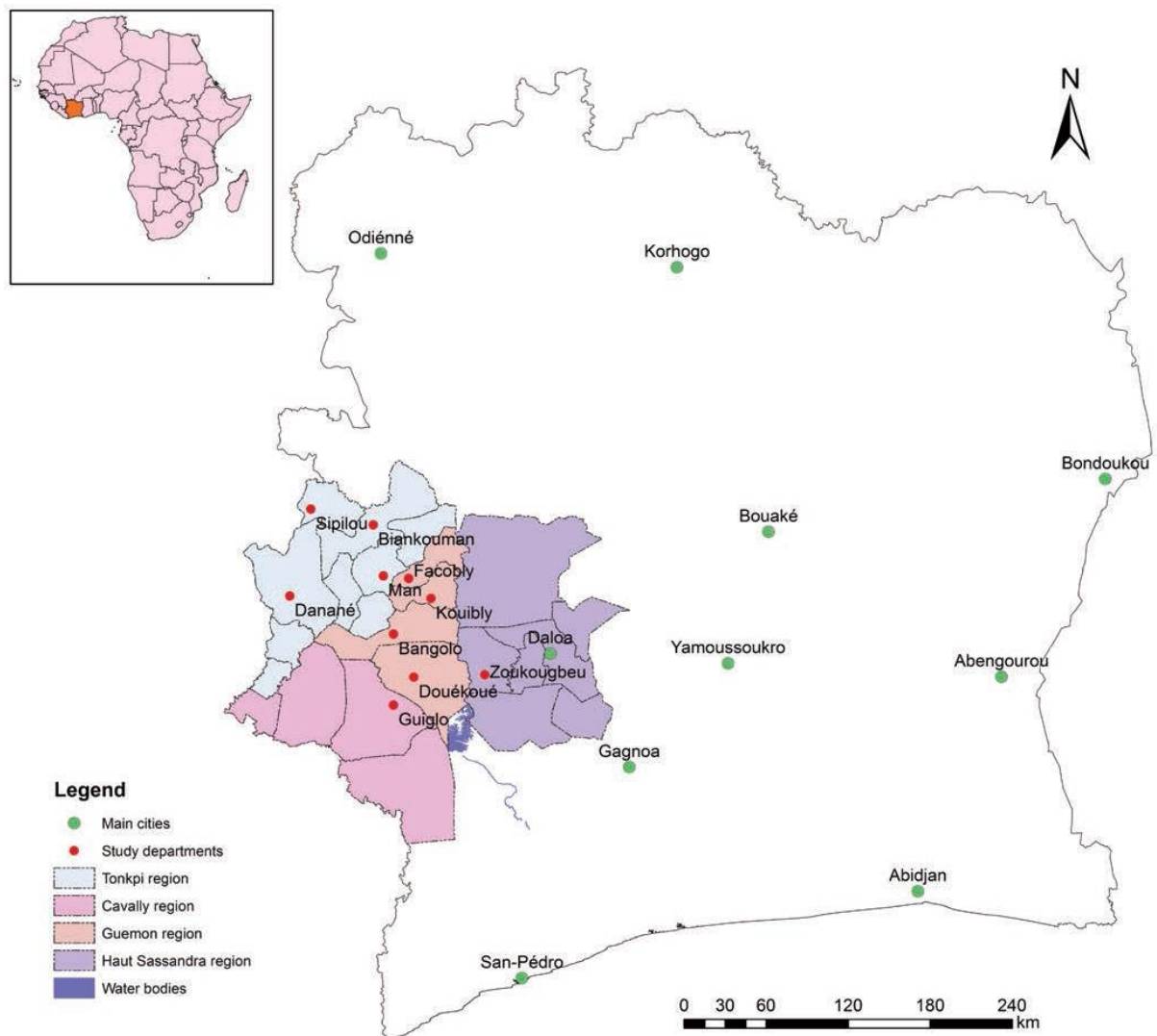


Figure 3.1: Map of Côte d’Ivoire with the four study regions in the western part of the country.

are mountainous areas with an average elevation ranging from 300 m above mean sea level (amsl) to slightly above 1000 m amsl (Raso *et al.*, 2005; Kouassi *et al.*, 2012; Gone Bi *et al.*, 2013). The rainy season occurs from March to October. The Haut-Sassandra region is located east of the Sassandra River and its average altitude ranges between 200 and 300 m amsl (Yapi *et al.*, 2014a). The climate is sub-equatorial, characterised by two rainy seasons. The long rainy season lasts from March to July and the short rainy season occurs in September and October.

People living in the western part of Côte d’Ivoire belong to two main ethnicities: Mandé and Krou. People are mainly engaged in subsistence agriculture (cassava, maize,

plantain and rice). Rice growing is the most important agricultural activity, leading to a high frequency of contact with water. There is also production of cash crops (coffee, cocoa and rubber cultivation) and a small forestry industry in the town of Man (Utzinger *et al.*, 2000).

Schistosomiasis, soil transmitted helminthiasis, malaria, giardiasis and amoebiasis are highly endemic in the study area (Raso *et al.*, 2005; Matthys *et al.*, 2006; Ouattara *et al.*, 2008; Silué *et al.*, 2008).

3.3.3. Parasitological survey

A cross-sectional parasitological survey was carried out in 264 schools from June to December 2011. The schools were selected based on accessibility by 4 wheel drive cars and number of registered children (≥ 200 pupils). Lists of schools and sketch maps of the four regions were used for planning the surveys. After receiving consent from the headmaster, teachers prepared class lists, including name, age and sex of all children. In each school, we aimed at selecting 50 children attending grades 4-6, as described elsewhere (Assaré *et al.*, 2014). In brief, children aged 13 years and above were selected from grades 4-6 until the number of children reached 50. In settings where less than 50 children in this age range were present, the sample was completed with younger children. Children with written informed consent from their parents or legal guardians were given a 125 mL plastic container and asked to return it with a small portion of their own stool. The containers were collected and labelled with unique identification numbers.

Stool specimens were transferred to central laboratories in Douékoué and Man and processed with the Kato-Katz technique (Katz *et al.*, 1972). Duplicate Kato-Katz thick smears were prepared from each stool specimen using 41.7 mg templates. After a clearing time of 60 min, the thick smears were examined under a microscope by one of five experienced laboratory technicians. *S. mansoni* eggs were counted and recorded. For quality control, 10% of the slides were selected (one slide chosen out of each 10 slides read) and re-examined the same day by a senior microscopist. In case of conflicting results, the slides were read a third time and the results discussed until agreement was reached (Speich *et al.*, 2015).

3.3.4. Climatic and environmental data

Geographical coordinates of each school were collected using a hand-held global positioning system (GPS) receiver (Garmin Etrex 30; Garmin, Olathe, KS, USA). Climatic data were obtained from readily available remote sensing sources (Table 1). Land surface temperature at day (LSTDay), land surface temperature at night (LSTNight) and rainfall estimate (RFE)

were obtained for the period of 2011-2012. Rainfall estimate data with an 8×8 km spatial resolution from Meteosat 7 satellite were obtained from the Africa Data Dissemination Service (<http://earlywarning.usgs.gov/adds/index.php>). Land surface temperature at day and night data were downloaded from the Moderate Resolution Imaging Spectroradiometer (MODIS) from the United States Geographical Survey - Earth Resources Observation and Science Data Center (<http://modis.gsfc.nasa.gov>).

3.3.5. Statistical analysis

Children were classified into three age groups (i.e. 8-12, 13-14 and 15- 19 years). Land cover was included into the model as categorical covariate. Continuous variables were standardised to mean zero, including standard deviation (SD). Pearson’s correlation was calculated between continuous variables and was further used to check for variables with a high correlation coefficient (>0.9) to avoid colinearity.

Table 3.1: Remote sensing data sources used for risk profiling of *Schistosoma mansoni* in western Côte d'Ivoire.

Source	Data type	Data period	Temporal resolution	Spatial resolution
MODIS ^a	LST ^g	03/2011-02/ 2012	8 days	1 km
MODIS ^a	NDVI ^h	03/2011-02/ 2012	16 days	1 km
MODIS ^a	Land cover	2001-2004	Year	1 km
WorldClim ^b	Elevation	2000	-	1 km
FEWS NET ^c	Rainfall	03/2011-02/ 2012	10 days	8 km
SWBD ^d	Water bodies	2000	-	30 m
ISRIC ^e	Soil types	-	-	8 km
Bayesian Kriging ^f	Improved sanitation	1991-2012	-	5 km
Bayesian Kriging ^f	Better drinking-water	1991-2012	-	5 km
LST _{Day} ^g	SD ^j of LST _{Day}	03/2011-02/ 2012		1 km
LST _{Night} ^h	SD ^j of LST _{Night}	03/2011-02/ 2012		1 km
diffLST ⁱ	LST _{Day} minus LST _{Night}	03/2011-02/ 2012		1 km
Rainfall	SD ^j of rainfall data	03/2011-02/ 2012		1 km

^aThe moderate resolution imaging spectroradiometer (MODIS; <https://mrtweb.cr.usgs.gov/>).

^bGlobal climate data (WorldClim) (<http://www.worldclim.org/current>).

^cThe famine early warning systems network (FEWS NET; <http://earlywarning.usgs.gov/adds/index.php>).

^dThe shuttle radar topography mission (SRTM) water body data (SWBD; <http://gis.ess.washington.edu/data/vector/worldshore/index.html>).

^eThe international soil reference and information center (ISRIC; <http://www.isric.org/data/isric-wise-derived-soil-properties-5-5-arc-minutes-global-grid-version-12>).

^fBased on household data from demographic and health surveys (DHS; <http://www.measuredhs.com>), multiple cluster indicator surveys (MICS; <http://www.childinfo.org/mics.html>), world health surveys (WHS; <http://www.who.int/healthinfo/survey/en/index.html>) and living standards measurement study (LSMS; <http://iresearch.worldbank.org/lsmssurveyFinder.htm>).

^gLand surface temperature at day.

^hLand surface temperature at night.

^hThe normalized difference vegetation index.

ⁱDifference between LSTDay and LSTNight

^jStandard deviation.

We implemented Bayesian variable selection to identify the best set of predictors. Briefly, normal mixture of inverse Gammas with parameter expansion (peNMIG) spike-and-slab priors was applied on the model (Scheipl *et al.*, 2012). We used mixed inverse Gamma distributions for the priors of the coefficients. One component (exclusion component) is a narrow spike around zero, while the other component (inclusion component) is a wide slab away from zero. For categorical variables, we applied a peNMIG prior that allows to simultaneously including or excluding all coefficients related with the categories of the same variable, by improving shrinkage properties (Scheipl *et al.*, 2012). We included the variables with the inclusion component predominant (*i.e.* a posterior probability higher than 50%) into our final geostatistical model. The details of the method have been described elsewhere (Lai *et al.*, 2013).

Bayesian geostatistical logistic regression models with spatially structured random effects were applied to obtain spatially explicit *S. mansoni* estimates. Specifically, we assumed that the number of positive individuals Y_i arises from a binomial distribution $Y_i \sim B_n(p_i, n_i)$, where $\text{logit}(p_i) = \beta_0 + \sum_{k=1} \beta_k \times X_i^{(k)} + \varepsilon_i + \phi_i$. n_i and p_i indicate the number of those examined and the probability of infection at location i ($i=1,2,\dots,L$). β_k , ε_i and ϕ_i represent the regression coefficient of the k^{th} covariate $X_i^{(k)}$, location-specific random effect and exchangeable non-spatial random effect, respectively. We assumed $\varepsilon \sim MVN(0, \Sigma)$ with a covariance function $\Sigma_{ij} = \sigma_{sp}^2 \exp(-\rho d_{ij})$, where d_{ij} is the Euclidean distance between location i and j , and ρ corresponds to the rate of correlation decay. We assumed an inverse gamma hyper-prior distribution for σ_{sp}^2 and a gamma hyper-prior distribution for ρ . The spatial range, which is considered as the minimum distance of the spatial correlation less than 10%,

can be calculated as $-\log(0.1)/\rho$. ϕ_i was assumed to follow a zero-mean normal distribution $\phi_i \sim N(0, \sigma_{nonsp}^2)$. We assigned the prior distributions as follows: $\beta_0, \beta_k \sim N(0, 100)$, $\sigma_{sp}^2 \sim IG(0.01, 0.01)$, $\sigma_{nonsp}^2 \sim IG(0.01, 0.01)$ and $\rho \sim G(0.01, 0.01)$. Markov chain Monte Carlo simulation was employed to estimate the model parameters in Openbugs version 3.0.2 (Imperial College London and Medical Research Council, London, UK) (Lunn *et al.*, 2009). Gelman and Rubin diagnostics was used to assess the convergence by the coda library in R (Gelman & Rubin, 1992; Plummer *et al.*, 2006). A 1×1 km grid was overlaid to the study region, resulting in 53,820 pixels. Bayesian kriging was done to predict the *S. mansoni* infection risk at the centroids of the grid's pixels.

3.3.6. Model validation

We randomly selected a subset of the data (training set), including approximately 80% of survey locations for model fitting and subsequently assessed the model performance on the remaining 20% (test set). Mean error (ME), that is the expectation of differences between the observed and predicted prevalence, and the percentage of observations included in Bayesian credible intervals (BCI) of various probability coverages of predictions on test set locations were calculated.

3.4. Results

3.4.1. Study cohorts

Sufficiently large stool samples were collected from 12,462 schoolchildren. There were 8151 (65.4%) males and 4311 (34.6%) females. The age ranged between 8 and 19 years; 1914 children (15.4%) were 8- 12 years old, 9043 (72.6%) were 13-14 years old and the remaining 1505 (12.0%) were 15-19 years old. Around half of the schools (n=131, 49.6%) were located in to the Tonkpi region. There were 113 schools (42.8%) in the Guemon region, while only 13 (4.9%) and 7 (2.7%) schools were included in the Haut-Sassandra and Cavally region, respectively.

3.4.2. Parasitological data

Among the 264 schools, 157 (59.5%) had a *S. mansoni* prevalence above 24%, 78 (29.5%) schools had a prevalence ranging between 10 and 24%, whilst the remaining 29 schools (11.0%) had a prevalence below 10%. The overall prevalence of *S. mansoni* was 39.9%. Boys

showed a statistically significantly higher prevalence of *S. mansoni* than girls (42.9% vs 34.2%; $\chi^2= 88.76$, $P<0.001$). The prevalence of infection was 33.5, 41.0 and 40.9% among children aged 8-12, 13-14 and 15-19 years, respectively. Figure 3.2 displays the *S. mansoni* infection prevalence in each of the 264 schools. At the unit of the school, the prevalence of *S. mansoni* ranged from 0 to 100%. High prevalence rates were predominantly found in the Tonkpi region. Moderate infection prevalences (10-24%) were mostly found in Gomon and Cavally regions. In the schools of Haut-Sassandra, the prevalence of *S. mansoni* was consistently below 24%.

3.4.3. Spatial statistical modelling and validation result

The Bayesian variable selection identified the following predictors: sex, age group, difference of LST between day and night (diffLST) and altitude. The Bayesian geostatistical logistic regression model was able to correctly estimate (within a 95% BCI) 81.2% for *S. mansoni* at the test locations. The ME was 4.6%, which means the model may underestimate the risk of *S. mansoni* infection.

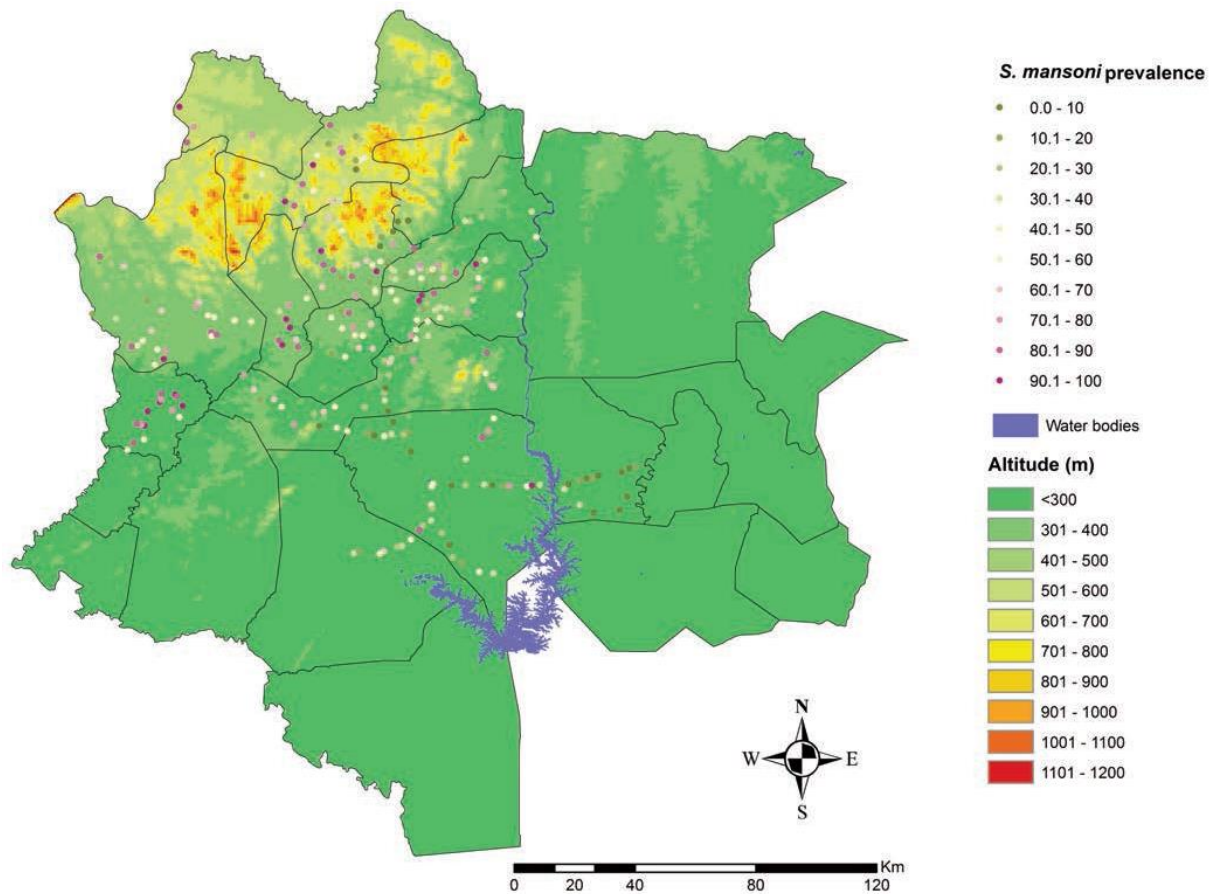


Figure 3.2: Observed *Schistosoma mansoni* infection prevalence in 264 schools in western Côte d'Ivoire, as assessed in a cross-sectional survey from June to December 2011.

3.4.4. Relationship between *Schistosoma mansoni* and environmental factors

Table 2 summarises the key findings with respect to the relationship between *S. mansoni* and demographic, environmental and climatic factors. Children from the oldest age group (15-19 years) had higher odds of *S. mansoni* infection compared to those aged 8-12 years (odds ratio (OR)=1.35, 95% BCI: 1.12; 1.65). We did not find significant difference of *S. mansoni* prevalence rates between children aged 13-14 years and 8-12 years. Boys had higher odds of *S. mansoni* infection than girls (OR=1.58, 95% BCI: 1.43; 1.73).

Altitude was negatively associated with the prevalence of *S. mansoni* (OR=0.49, 95% BCI: 0.28; 0.70). We found a positive correlation between diffLST and *S. mansoni* infection (OR=1.36, 95% BCI: 1.12; 1.60).

Table 3.2: Posterior summaries (median and 95% Bayesian credible interval) of odds ratios of the geostatistical model parameters for *Schistosoma mansoni* infection.

Variable	Multivariable non-spatial	Binary non-spatial	Geostatistical model
Sex	1.43 (1.32; 1.55)*	1.45 (1.34; 1.55)*	1.58 (1.43; 1.73)*
Age group 1	1.36 (1.22; 1.51)*	1.38 (1.25; 1.54)*	1.15 (0.99; 1.35)
Age group 2	1.34 (1.16; 1.54)*	1.38 (1.20; 1.58)*	1.35 (1.12; 1.65)*
Altitude	1.01 (0.98; 1.05)	1.03 (0.99; 1.06)	0.49 (0.28; 0.70)*
diffLST	1.00 (0.96; 1.04)	1.01 (0.98; 1.05)	1.36 (1.12; 1.60)*
Range			181.31 (72.98; 460.24)
σ_{sp}^2			3.03 (1.36; 8.26)
σ_{nonsp}^2			0.88 (0.63; 1.14)

diffLST, difference between land surface temperature at day and at night. *Significant correlation based on 95% confidence interval or 95% Bayesian credible interval.

3.4.5. Spatial analysis of *Schistosoma mansoni* infection

The main results derived from the multivariable and the binary nonspatial logistic regression models are summarised in Table 2. The nonspatial multivariable logistic regression model revealed a significant association between the prevalence of *S. mansoni* and sex (OR=1.43, 95% BCI: 1.32; 1.55), and age (age group 13-14 years, OR=1.36, 95% BCI: 1.22; 1.51; and age group 15-19 years, OR=1.34, 95% BCI: 1.16; 1.54 compared to age group 8-12 years). There was no association between *S. mansoni* infection and altitude and diffLST. The binary non-spatial model showed that disease transmission was significantly associated with sex (OR=1.45, 95% BCI: 1.34; 1.55) and age (age group 13-14 years OR=1.38, 95% BCI: 1.25; 1.54; age group 15- 19 years, OR=1.38, 95% BCI: 1.20; 1.58 compared to age group 8-12 years). However, there was no association between *S. mansoni* infection and climatic and environmental factors. Table 2 also shows the principal findings of the Bayesian geostatistical logistic regression model. Age, sex and diffLST were positively correlated with *S. mansoni*, whilst altitude showed a significant negative association with *S. mansoni* infection prevalence.

3.4.6. Spatial prediction of *Schistosoma mansoni* infection

Figure 3.3 shows the predicted *S. mansoni* infection prevalence in the study area for boys and girls with different age groups, and Figure 3.4 displays the corresponding prediction uncertainty. A very high prevalence of *S. mansoni* (>50%) was predicted predominantly in the Tonkpi region. Some focal high-prevalence schools were also predicted in central Gomon and northern Haut-Sassandra regions.

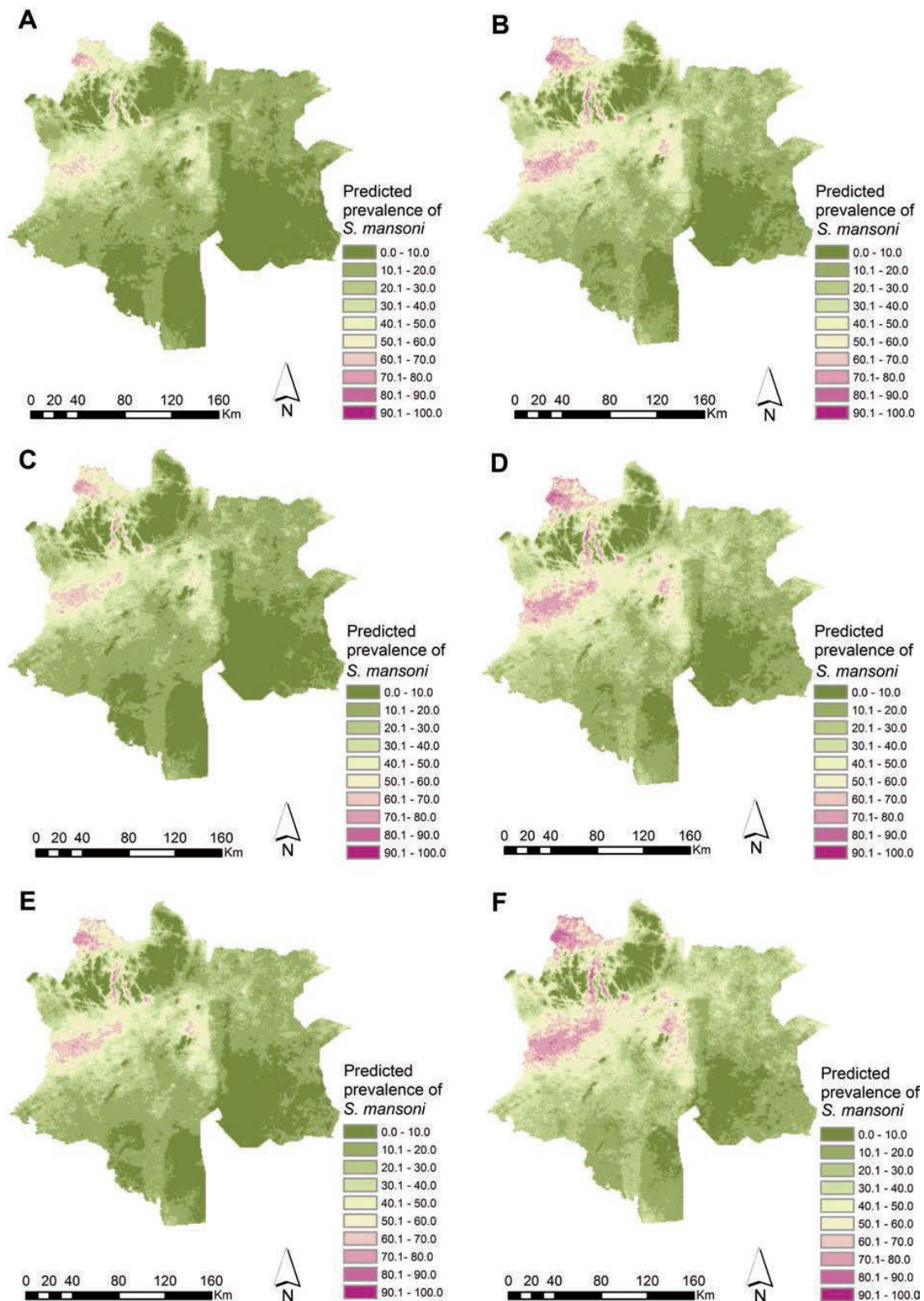


Figure 3.3: Predicted *Schistosoma mansoni* infection prevalence in the four study regions of western Côte d'Ivoire.

Predicted prevalence among girls aged 8-12 years (A), boys aged 8-12 years (B), girls aged 13-14 years (C), boys aged 13-14 years (D), girls aged 15-19 years (E) and boys aged 15-19 years (F).

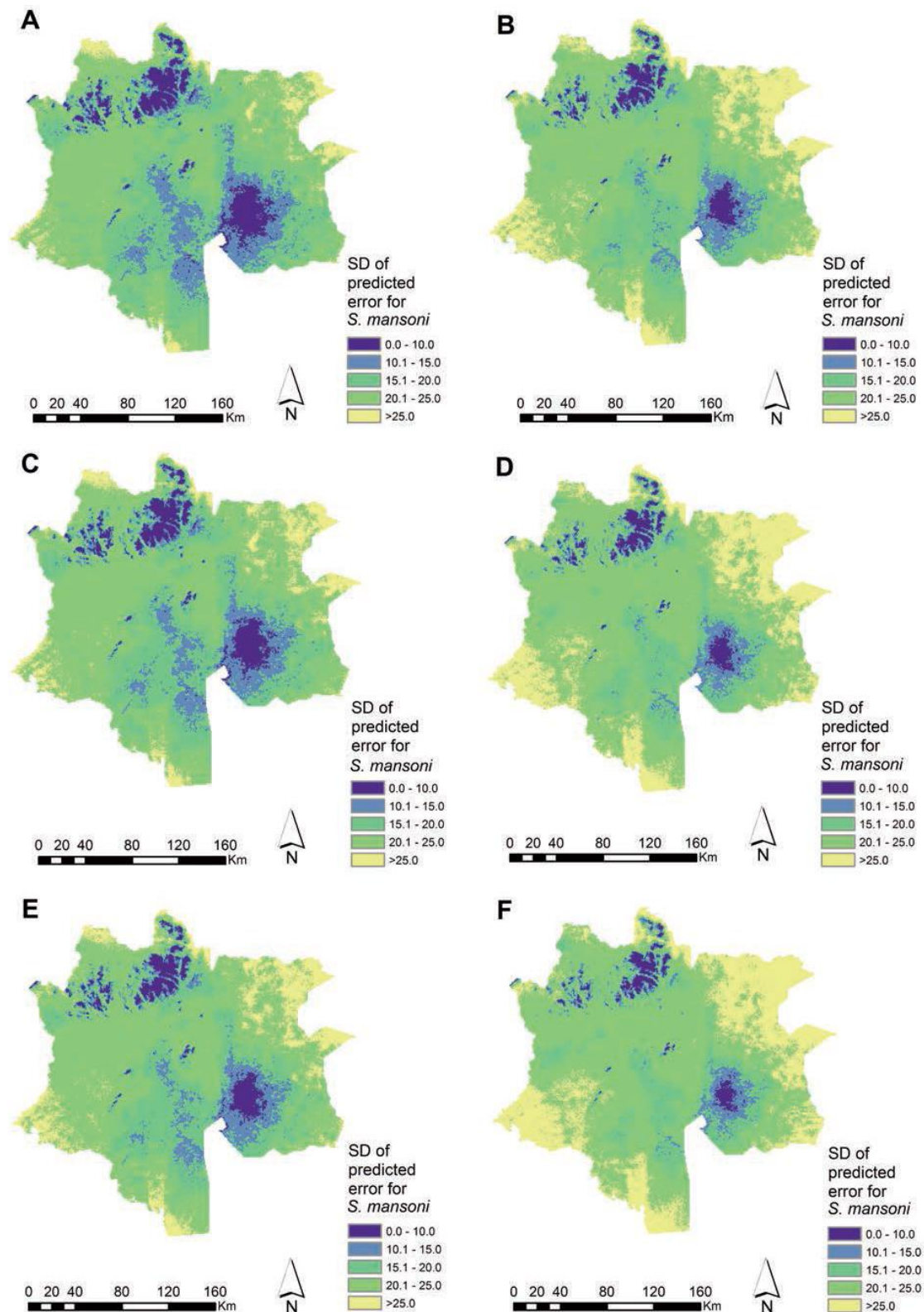


Figure 3.4: Prediction uncertainty of the posterior predictive distribution of *Schistosoma mansoni* infection prevalence in western Côte d'Ivoire.

Standard deviation (SD) of the posterior predictive distribution among girls aged 8-12 years (A), boys aged 8-12 years (B), girls aged 13-14 years (C), boys aged 13-14 years (D), girls aged 15-19 years (E) and boys aged 15-19 years (F).

Moderate prevalences of *S. mansoni* infection according to SCORE definition (10-24%) were predicted for large parts of Cavally, Haut-Sassandra and Gomon regions. Low prevalences (<10%) were predicted for East Cavally, south-western Haut-Sassandra and a small area in the northern part of Gomon region. The predicted prevalence of *S. mansoni* for boys was higher than the predicted prevalence for girls.

3.5. Discussion

Schistosomiasis remains of considerable public health importance in sub-Saharan Africa and a precise knowledge of high-risk areas is required for spatial targeting of control interventions. Within the frame of a large eligibility survey to identify schools where the prevalence of *S. mansoni* among school-aged children is 10-24%, more than 12,000 children were screened by duplicate Kato-Katz thick smears in four regions of western Côte d'Ivoire. We adhered to the SCORE harmonization protocol and aimed for children aged 13-14 years, but in order to have sufficient children per school, children's age finally ranged between 8 and 19 years. We found an overall prevalence of *S. mansoni* of 39.9%. Our results therefore confirm that *S. mansoni* is highly endemic in the western part of Côte d'Ivoire (Utzing et al., 2000; Raso et al., 2005; Beck-Worner et al., 2007), and that the geographical extent of the problem is larger than previously thought. Our study also confirms that schistosomiasis is highly focal; (Ratard et al., 1990; Lengeler et al., 2002b; Raso et al., 2005; Hodges et al., 2012). Indeed, while in some schools no child was infected with *S. mansoni*, more than half of the children were infected in other schools. High prevalences of *S. mansoni* were mostly found in the northern Tonkpi region, which is in line with results from previous studies (Roux et al., 1980; Utzinger et al., 2000; Keiser et al., 2002; Matthys et al., 2007). In the schools located in the Cavally and Gomon regions, *S. mansoni* infection prevalences mainly ranged between 10 and 45%. The prevalences of *S. mansoni* in the schools in the southern Haut-Sassandra region were consistently below 25%. Bayesian spatial statistical analysis showed that demographic, environmental and climatic covariates were useful predictors explaining the spatial distribution of *S. mansoni* infection prevalence. Altitude was negatively associated with the distribution of *S. mansoni*. These observations confirm results from previous digital elevation models and Bayesian geostatistical analysis (Raso et al., 2005; Beck-Worner et al., 2007). Indeed, it has been shown that children living in western Côte d'Ivoire at locations below 400 m amsl were at a 5-fold higher risk of *S. mansoni* infection when compared with those living at higher locations (Raso et al., 2005). However, the altitude threshold limit for *S. mansoni* transmission varies from one study setting to another (Ghebreyesus et al., 2002;

Kabatereine et al., 2004; Rubaihayo et al., 2008). Our study also revealed that a diffLST was correlated with the prevalence of *S. mansoni* infection. Several epidemiological studies using Bayesian geospatial, Gaussian and Poisson modelling documented that LSTDay was negatively associated with *S. mansoni*, while LSTNight was positively associated with the prevalence of *S. mansoni* (Hu et al., 2013a; Hu et al., 2013b; Schur et al., 2013; Scholte et al., 2014). In contrast, previous geostatistical analysis from the Tonkpi region found no relationship between *S. mansoni* infection and diffLST (Raso et al., 2005). However, a limitation of the latter study was that all surveyed schools were located in the same region with similar environmental and climatic features such as diffLST.

Environmental factors such as elevation influence flow velocity of rivers and LST shapes temperature of freshwater bodies. In turn, these factors impact on the presence of intermediate host snails, the parasite development within the snails and the infectivity of *Schistosoma cercariae* (Foster, 1964; Appleton, 1978; Kloos et al., 2001; Malone, 2005; McCreesh and Booth, 2014). A possible explanation for the observed higher prevalences of *S. mansoni* infection in the lower parts of the mountainous Tonkpi region may be the favourable temperature and velocity of rivers for *B. pfeifferi* (Shiff and Husting, 1966). Indeed, recent malacological studies carried out in Tonkpi region confirmed a high population density of *B. pfeifferi* (Tian-Bi et al., 2013; Yapi et al., 2014b). The lower *S. mansoni* prevalences in the Haut-Sassandra region might be due to less favourable environmental conditions for the development of *B. pfeifferi*. Instead, the conditions in this area seem to rather suit the development of *B. globosus*, an important intermediate host snail of *S. haematobium* (Cadot et al., 1998; Fournet et al., 2004).

A limitation of our study is that no intermediate host snails were collected. Moreover, only one stool sample per individual was subjected to duplicate Kato-Katz thick smears. This diagnostic approach has a low sensitivity for *S. mansoni*, particularly for detection of light-intensity infections (Engels et al., 1996; Utzinger et al., 2001; Booth et al., 2003; Enk et al., 2008). Few schools were surveyed in Cavally and Haut- Sassandra regions. The relatively small number of survey locations in this area may have negatively affected the prediction accuracy. Lastly, our final model did not include rainfall and socioeconomic status, as these factors were not picked up by our variable selection procedures. However, both variables play a role for snail breeding and human infection as shown before (Raso et al., 2005; Muhumuza et al., 2009; Xue et al., 2011).

3.6. Conclusion

In conclusion, pursuing a Bayesian geostatistical analysis using a large set of georeferenced *S. mansoni* prevalence data from a SCORE eligibility survey (Assaré et al., 2014) allowed risk profiling of *S. mansoni* in four regions of western Côte d'Ivoire. The generated risk maps have already been utilised by the national schistosomiasis control programme. As control efforts in the western part of Côte d'Ivoire and elsewhere in the country move ahead, it will be very interesting to monitor changes over time.

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4. Paper 3 - Sustaining the control of *Schistosoma mansoni* in western Côte d'Ivoire: baseline findings before the implementation of a randomized trial

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4.1. Abstract

We report baseline findings before the implementation of a 4-year intervention trial designed to assess the impact of three different school-based treatment schedules with praziquantel to sustain the control of intestinal schistosomiasis. The baseline survey was conducted in 75 schools of western Côte d'Ivoire previously identified with moderate *Schistosoma mansoni* endemicity (prevalence: 10-24% in children aged 13-14 years). Three stool samples collected over consecutive days were subjected to duplicate Kato-Katz thick smears each. A questionnaire was administered to collect village-specific information that is relevant for schistosomiasis transmission. Overall, 4,953 first graders (aged 5–8 years) and 7,011 school children (aged 9–12 years) had complete parasitologic data. The overall prevalence of *S. mansoni* was 5.4% among first graders and 22.1% in 9- to 12-year-old children. Open defecation was practiced in all villages. The current baseline findings will be important to better understand the dynamics of *S. mansoni* prevalence and intensity over the course of this trial that might be governed by village characteristics and specific treatment interventions.

4.2. Introduction

Schistosomiasis, a water-associated disease, remains a relevant public health problem in the tropics and subtropics. Indeed, schistosomiasis affects more than 250 million people with an estimated global burden of 3.9 million disability adjusted life years (Murray et al., 2012; Hotez et al., 2014). In 2013, some 121 million school-aged children were considered at risk of schistosomiasis, with more than 90% of them concentrated in sub-Saharan Africa (WHO, 2015). In this region, approximately one-third of the schistosomiasis cases are caused by the species *Schistosoma mansoni* (van der Werf et al., 2003).

Since the mid-1980s, the World Health Organization (WHO) recommends preventive chemotherapy, that is, the large scale population-based mass drug administration (MDA) of praziquantel, as the main pillar of schistosomiasis control (WHO, 1985). The target is to treat at least 75% and up to 100% of school aged children at risk of schistosomiasis with praziquantel (WHO, 2002; WHO, 2013). In 2012, numerous institutions and private organizations approved and decided to support this goal (WHO, 2012a). According to WHO guidelines, the frequency of treatment in the school aged population (children aged 5–14 years regardless of whether they are enrolled in school) is 1) once every year in high-risk communities (prevalence: $\geq 50\%$ measured by parasitologic methods); 2) once every second

year in moderate risk communities (prevalence: 10–49%); and 3) twice during primary school age in low-risk communities (prevalence: < 10%) (WHO, 2013). To strengthen the current evidence base for program decisions about preventive chemotherapy to gain and sustain the control of schistosomiasis, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE; <http://score.uga.edu/>) designed a multi-country study with several treatment arms implemented over multiple years (Assaré et al., 2014; Colley, 2014).

In contrast to other schistosomiasis-endemic parts of the world where considerable progress in the fight against schistosomiasis has been achieved over the past decades (e.g., Brazil and China) (Utzinger et al., 2005; Bergquist, 2008), control efforts in sub-Saharan Africa were less successful, partially explained by low coverage and rapid reinfection rates after MDA campaigns (Danso-Appiah and De Vlas, 2002; Clements et al., 2009; WHO, 2015). To deepen our understanding why schistosomiasis control interventions, including preventive chemotherapy, are more or less successful, it is important to consider determinants of disease transmission, such as hydrogeographic features, access and use of clean water, improved sanitation and hygiene, and socioeconomic characteristics of local communities (Steinmann et al., 2006; WHO., 2012b; Knopp et al., 2013; Grimes et al., 2014).

This article describes the baseline parasitologic situation and village characteristics of the 75 communities in western Côte d’Ivoire that were randomized to one of the three intervention arms of a SCORE study to determine the effect of different treatment schedules to sustain schistosomiasis control in moderate endemicity areas (Assaré et al., 2014). In each school, some 100 children (usually 9-12 years) submitted three consecutive stool samples that were subjected to duplicate Kato-Katz thick smears each. We also compared our *S. mansoni* prevalence data with results from a previous large-scale eligibility survey while screening 50 children aged 13–14 years with a single stool sample subjected to duplicate Kato-Katz thick smears. We show how fragile the categorization into risk communities is, based on simple prevalence thresholds, as it depends on the age of subjects screened, sampling efforts, diagnostic approach, among other issues.

4.3. Materials and methods

4.3.1. Ethics statement

Ethical approval for this study was obtained from the ethics committees of the Ministry of Public Health in Abidjan, Côte d’Ivoire (reference no. 1994 MSHP/CNER) and the ‘Ethikkommission beider Basel’ in Basel, Switzerland (reference no. EKBB 297/10). The

purpose of the study was explained to education and health authorities. An information sheet was delivered to participating school children and written informed consent was obtained from their parents or guardians. At the end of the baseline parasitologic survey, all children aged 5–15 years living in the study area were offered praziquantel treatment (40 mg/kg) provided free of charge by the “Programme National de Lutte contre la Schistosomiase, les Géohelminthiases et la Filariose Lymphatique.” Praziquantel treatment was given to children using the WHO dose pole (Montresor et al., 2002).

4.3.2. Study area and population

As shown in Figure 4.1, the study is being implemented in four regions of western Côte d’Ivoire: Cavally, Guemon, Tonkpi, and Haut-Sassandra, extending from 06°28’47.5” to 07°52’10.0” N latitude and from 06°44’09.8” to 08°21’30.0” W longitude. Previous studies showed that *S. mansoni* is highly endemic in this area, while *S. haematobium* coexists in some areas (Doumenge et al., 1987; Utzinger et al., 2000; Fournet et al., 2004; Raso et al., 2005; Chammartin et al., 2014). Previous malacologic surveys revealed that *Biomphalaria pfeifferi* and *Bulinus globosus* act as intermediate host snail of *S. mansoni* and *S. haematobium*, respectively (Cadot et al., 1998; Fournet et al., 2004; Matthys et al., 2007; Yapi et al., 2014a; Yapi et al., 2014b). In a cross-sectional survey carried out between June 19 and August 22, 2011, and between December 4 and 22, 2011, to identify communities eligible to participate in this SCORE study, the *S. mansoni* prevalence was determined in 264 schools (Assaré et al., 2014). In each school, 50 children aged 13–14 years were examined by duplicate Kato-Katz thick smears on a single stool sample. *S. mansoni* prevalence rates above 24% were mainly observed in Tonkpi region, while schools with prevalence of infection ranging between 10% and 24% were predominantly found in Gomon, Cavally, and Haut-Sassandra (Assaré et al., 2015). Those 75 villages where the *S. mansoni* prevalence ranged between 10% and 24% and that fulfilled other inclusion criteria were eligible for the SCORE trial. Villages were randomized into one of three treatment arms. This article describes the baseline situation in the 75 schools including important village characteristics.

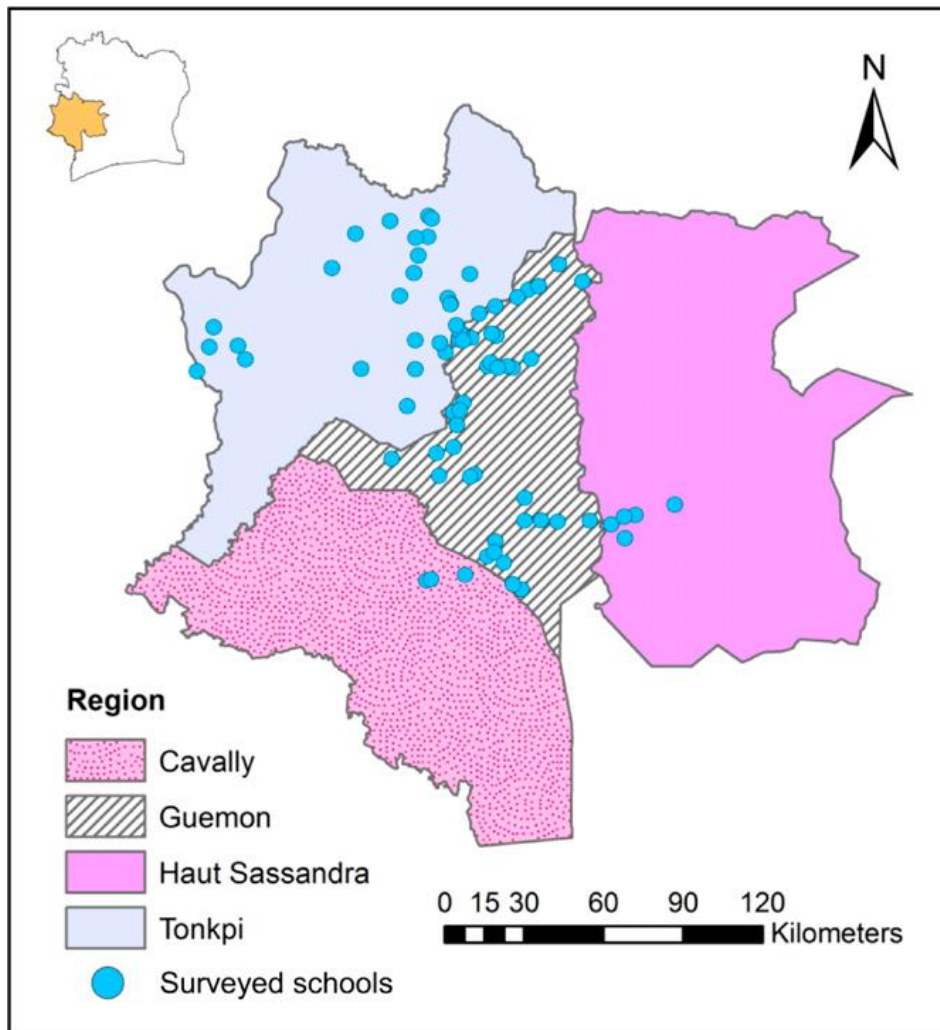


Figure 4.1: Study area in western Côte d'Ivoire showing schools surveyed at the eligibility survey (June–August 2011 and December 2011) and at the baseline survey (December 2011 to February 2012) in blue circles.

4.3.3. Field and laboratory procedures

The baseline survey in the 75 schools was conducted from December 4 to 22, 2011, and from January 26 to February 27, 2012. In the first step, teachers prepared lists with the name, sex, and age of children enrolled in their classes. Subsequently, in each school, 100 children (usually aged 9–12 years) from grades 2–6 and up to 100 children from grade 1 were randomly selected from the lists. In case insufficient numbers of children were available in the desired age range, older children were invited to participate. The selected children received detailed information and an informed consent sheet, and they were asked to have the consent sheet signed by their parents or legal guardians (Assaré et al., 2014). Children with written informed consent were given a 125-mL plastic container and asked to provide a portion of their own fresh morning stool the next day. First-grade children were asked for a

single stool sample, while the other children were invited to submit stool samples on three consecutive days. Children's parents and guardians were asked to make sure that their children collected their own stool. Returned stool containers were collected and identified with unique codes by experienced fieldworkers and transferred to nearby laboratories for diagnostic work-up.

In the laboratories, stool samples were processed using the Kato-Katz technique, with a standard 41.7-mg plastic template (Katz et al., 1972). From each stool sample, duplicate Kato-Katz thick smears were prepared on two microscope slides. After a clearing time of at least 60 minutes, the thick smears were examined by experienced laboratory technicians under a light microscope at low magnification. Eggs of *S. mansoni* and soil-transmitted helminths (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) were counted and recorded for each species separately. For quality control, 10% of the slides were randomly selected and reexamined by a senior laboratory technician. If there were discrepancies between the two results (e.g., positive versus negative result, or counts differing by more than 20%), the respective slides were read again and the results discussed until agreement was reached.

4.3.4. Assessment of village characteristics

In parallel to the parasitologic survey, a questionnaire on factors that might influence *S. mansoni* transmission was administered to school directors and village leaders. The questionnaire included six main sections pertaining to 1) demographics (i.e., village name, number of households and individuals); 2) water-related activities in the population (i.e., fishing, cleaning, and irrigated rice farming); 3) health system indicators (i.e., presence and type of health facility, availability and quality of praziquantel and artemisinin-based combination therapy [ACT]); 4) water bodies (i.e., number of perennial and seasonal water courses/stagnant water bodies); 5) water use (i.e., water sources used for drinking, washing, and bathing); and 6) defecation behavior (i.e., open defecation, availability and use of sanitation facilities).

4.3.5. Statistical analysis

Data were entered into a Microsoft Excel workbook 2010 (Microsoft Corporation, Redmond, WA). Statistical analyses were done with STATA (version IC13.1; Stata Corporation, College Station, TX). The prevalence of *S. mansoni* infection from the eligibility survey was estimated based on the results from duplicate Kato-Katz thick smears from a single stool sample from children aged 13–14 years (Assaré et al., 2014). For the current analysis of the baseline

survey, two groups of children were considered: 1) all children aged 9–12 years who had at least four Kato-Katz thick smears examined after three consecutive days of stool sampling and 2) all first-grade children who provided a single stool sample and had one or two Kato-Katz thick smears examined. Two different prevalence estimates were calculated for the 9- to 12-year-old children at the baseline survey: 1) to render the sampling effort and prevalence comparable to the eligibility survey, the *S. mansoni* prevalence was calculated based on duplicate Kato-Katz thick smear results from the first stool sample and 2) to allow for a more accurate prevalence estimate, the *S. mansoni* prevalence was calculated from a minimum of four Kato-Katz thick smears from at least two consecutive stool samples. For the first-grade children, the *S. mansoni* prevalence was estimated based on at least one Kato-Katz thick smear from the single stool sample. Low-, moderate-, and high-endemicity areas were defined according to WHO (WHO, 2013) at prevalence thresholds of < 10%, 10–49%, and \geq 50%, respectively, and according to SCORE at prevalence thresholds of < 10%, 10–24%, and > 24%, respectively (WHO, 2002; Assaré et al., 2014).

The arithmetic mean (AM) number of eggs per gram of stool (EPG) for *S. mansoni* was calculated from all available Kato-Katz thick smear readings per individual. On the basis of AM EPGs of each individual, infection intensity was determined according to WHO guidelines: 1) light (1–99 EPG); 2) moderate (100–399 EPG); and 3) heavy infections (\geq 400 EPG) (WHO, 2002).

Water use and defecation behavior as coded in the questionnaire (i.e., never = 0, rarely = 1, often = 2, and always = 3) was simplified and used as a binary variable (i.e., 0 = not practiced, \geq 1 = practiced). In addition, mean prominence values based on the four code categories (sum of the observed code values divided by four) are provided.

4.4. Results

4.4.1. Characteristics of study population

As shown in Figure 4.2, a total of 12,431 children were invited to participate at the baseline survey. There were 7,478 children aged 9–12 years and 4,953 first graders. Among the 9- to 12-year old children, 467 were excluded, because they did not match the specified age group (N = 168), failed to provide even a single stool sample (N = 5), or had less than four Kato-Katz thick smears (N = 294). A total of 6,694 children aged 9– 12 years submitted a stool sample on day 1 and 6,384 and 6,402 stool samples were submitted on days 2 and 3, respectively. At least four Kato-Katz thick smear results were available from 7,011 children aged 9–12 years and at least one Kato-Katz thick smear was available from 4,953 first

graders. These two groups were included into the main analysis of the baseline survey. Their mean age was 10.5 years and 6.5 years, respectively, and the sex ratio for boys to girls was 1.4:1.0 and 1.3:1.0, respectively.

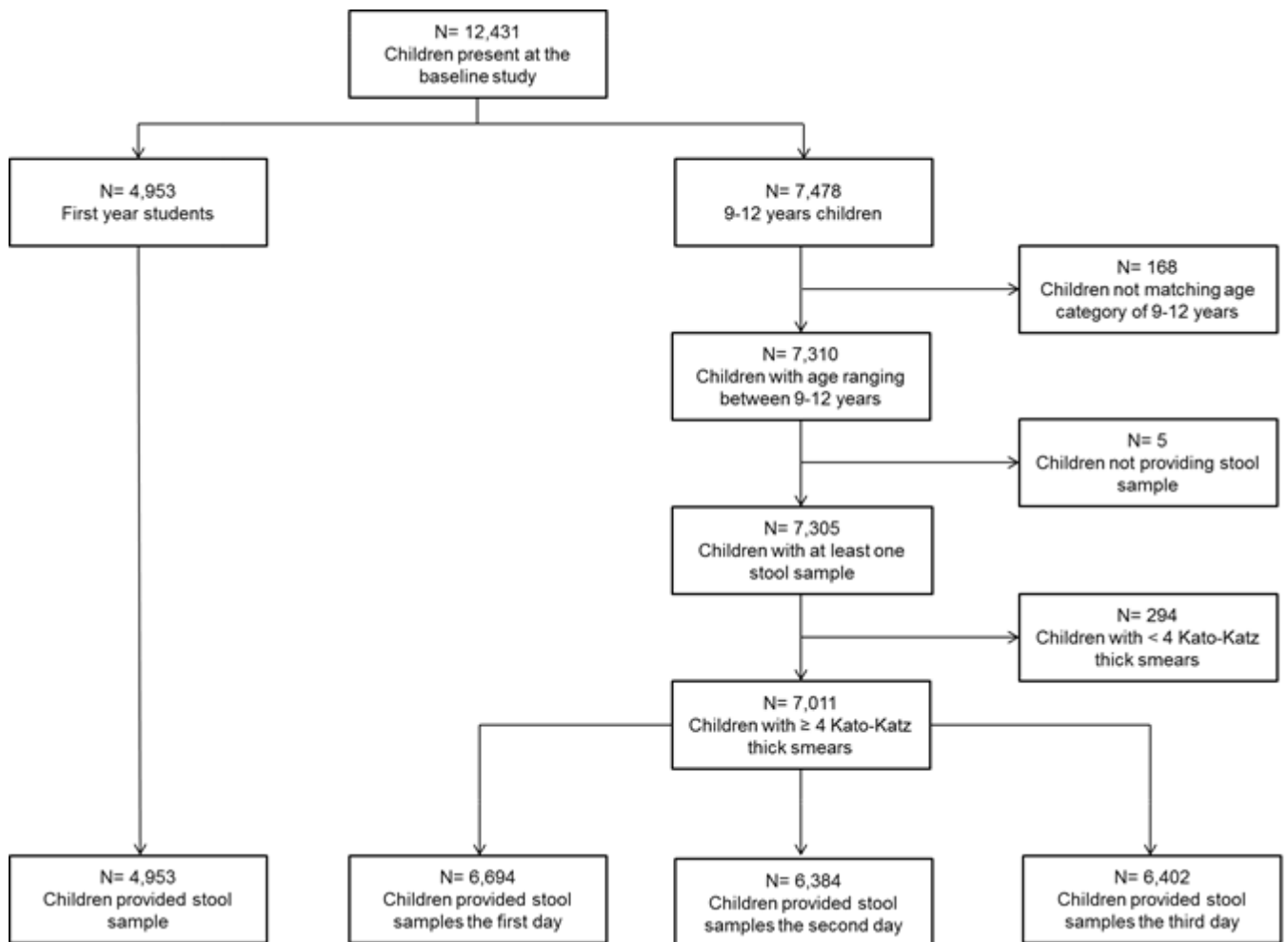


Figure 4.2: Study participation at the baseline survey conducted in 75 schools in western Côte d’Ivoire in December 2011 to February 2012.

4.4.2. *S. mansoni* and soil-transmitted infections

Table 4.1 summarizes *S. mansoni* prevalence and intensity of infection and prevalence of soil-transmitted helminths. Examination of at least four Kato-Katz thick smears per child revealed that among the 7,011 children aged 9–12 years, 1,547 (22.1%) were infected with *S. mansoni*. The prevalence ranged from 1.0% to 54.0% at the unit of the school and was significantly higher among boys (24.3%) than girls (18.8%) ($\chi^2 = 29.91$, $P < 0.001$). Among

Table 4.1: Prevalence and intensity of *Schistosoma mansoni* infection in first year and 9- to 12-year-old school children and prevalence of soil-transmitted helminth infections at the baseline survey conducted between December 2011 and February 2012 of a SCORE study in western Côte d’Ivoire

Variable	First-year schoolchildren	9- to 12-year-old schoolchildren
No. of individuals examined	4,953	7,011
No. of children infected (%)		
<i>S. mansoni</i>	269 (5.4)	1,547 (22.1)
<i>T. trichiura</i>	27 (0.6)	221 (3.2)
<i>A. lumbricoides</i>	15 (0.3)	66 (0.9)
Hookworm	6 (0.1)	95 (1.4)
Intensity of <i>S. mansoni</i> infection *		
Arithmetic mean EPG (95% CI)	10 (6.7-13.4)	20.4 (17.3-23.4)
Light infection (%)	73.2	80.9
Moderate infection (%)	21.4	14.2
Heavy infection (%)	7.7	4.9

CI = confidence interval; EPG = eggs per gram of stool; SCORE = Schistosomiasis Consortium for Operational Research and Evaluation.

*Light infection, 1–99 EPG; moderate infection, 100–399 EPG; heavy infection, \geq 400 EPG.

the 4,953 first graders, a *S. mansoni* infection was found in 269 children (5.4%). For this group, the prevalence at the unit of the school ranged between 0% and 20.9%. There was no significant difference by sex ($\chi^2 = 0.98$, $P = 0.321$).

In both age groups, the majority of children had light intensity infections, but the proportions of children with heavy infections were higher in first graders compared with 9- to 12-year-old children (7.7% versus 4.9%). Among 9- to 12-year-old children, the overall prevalence of *T. trichiura*, hookworm, and *A. lumbricoides* was 3.2%, 1.4%, and 0.9%, respectively. The corresponding values among first graders were 0.6%, 0.1%, and 0.3% respectively.

4.4.3. *S. mansoni* prevalence at the eligibility and baseline surveys

The overall *S. mansoni* prevalence based on the results from duplicate Kato-Katz thick smears from a single stool sample was 15.8% (95% confidence interval [CI], 14.8–16.8%) in the 12,110 children aged 13–14 years who participated in the eligibility survey and 13.0% (95% CI, 11.4–14.7%) in the 6,694 children aged 9–12 years who were surveyed at day 1 of the baseline survey. Considering the results of at least four Kato-Katz thick smears from 7,011 children, the overall *S. mansoni* prevalence at baseline was 22.1% (95% CI, 19.5–24.4%). Figure 4.3 shows that the average *S. mansoni* infection prevalence was lowest at the baseline survey considering duplicate Kato-Katz thick smears, followed by the eligibility survey, and the baseline survey with a diagnostic effort of at least quadruplicate Kato-Katz thick smears. Figure 4.4 shows the difference of the *S. mansoni* prevalence in the 75 schools compared

between eligibility survey considering two Kato-Katz thick smears and baseline survey considering at least four Kato-Katz thick smears. Overall, the prevalence in the eligibility survey was 39.9% lower than in the baseline survey. The prevalence of *S. mansoni* was significantly higher in five schools, while significantly lower rates were observed in three schools (Table 4.2). Among the 75 schools, 75 (100%) and 65 (86.7%) schools at the eligibility and baseline surveys, respectively, matched the WHO criteria of moderate endemicity (*S. mansoni* prevalence: 10–49%). In terms of target endemicity cut-offs defined by SCORE, by definition, all 75 schools fulfilled the target criteria of moderate endemicity (*S. mansoni* prevalence: 10–24%) at the eligibility survey, but only 40 schools (53.4%) remained in this category in the baseline survey using at least quadruplicate Kato-Katz thick smear results, while 28 schools (37.3%) had prevalences above 24% and seven schools showed prevalences below 10%. Among the 28 schools that showed a *S. mansoni* prevalence above the SCORE preset maximum level at baseline, three had prevalences above 50%.

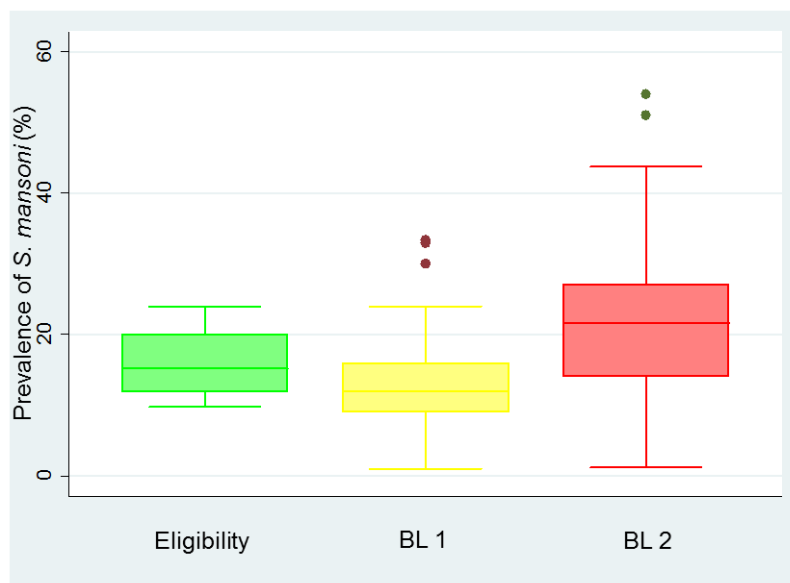


Figure 4.3: *Schistosoma mansoni* prevalence in children aged 13–14 years at the eligibility survey and in children aged 9–12 years at the baseline (BL) survey.

Eligibility: *S. mansoni* prevalence in 13- to 14-year-old children, according to results from duplicate Kato-Katz thick smears examined at the eligibility survey. BL1: *S. mansoni* prevalence in 9- to 12-year-old children, according to results from duplicate Kato-Katz thick smears examined from day 1 stool samples at the baseline survey. BL2: *S. mansoni* prevalence in 9- to 12-year-old children, according to the results from at least four Kato-Katz thick smears per child at the baseline survey.

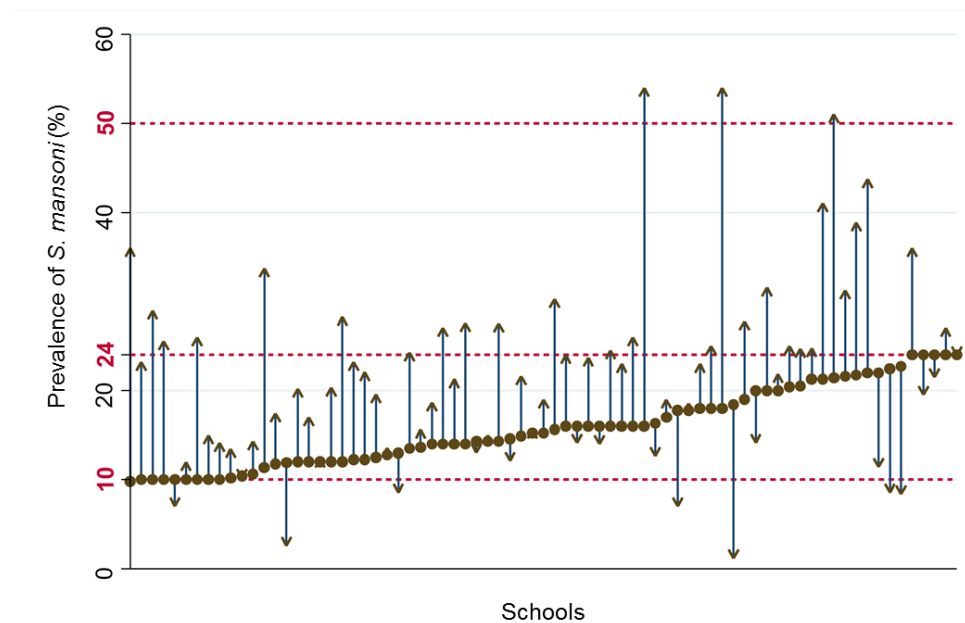


Figure 4.4: Dynamics of the *Schistosoma mansoni* prevalence in 75 schools from eligibility (points) to baseline (BL2: *S. mansoni* prevalence in 9- to 12-year-old children, according to results from at least four Kato-Katz thick smears per child at the baseline survey; arrow head) surveys.

A 10–24% prevalence determined at the eligibility survey was the defined target endemicity level of moderate prevalence for this Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) project. A prevalence of 10–49% is defined as moderate endemicity by criteria of the World Health Organization (WHO).

Table 4.2: Schools where significant changes have been observed in the *Schistosoma mansoni* prevalence comparing data from the eligibility and baseline surveys of a SCORE study in western Côte d’Ivoire

School	Eligibility		Baseline		Change (%)
	Prevalence (%)	95% CI	Prevalence (%)	95% CI	
Kassiapleu	10.0	1.4-18.6	29.0	20.0-38.0	+190.0
Gohouo-Zibiao	10.0	1.4-18.6	28.1	20.7-35.5	+180.8
Voungoué	11.4	1.6-21.1	33.7	23.9-43.5	+196.6
Glaou	18.0	7.0-29.0	39.7	31.7-47.8	+120.7
Kiéfé I	18.0	7.0-29.0	37.3	30.7-44.3	+107.2
Pona 2	18.4	5.5-31.3	1.2	-0.6-3.8	-93.5
Pinhou 1	22.0	10.1-33.9	4.1	1.1-7.1	-81.5
Guinglo-Zia	22.5	10.3-34.6	5.2	1.7-8.7	-76.9

CI = confidence interval; SCORE = Schistosomiasis Consortium for Operational Research and Evaluation.

4.4.4. Demographic and environmental characteristics of local communities

Table 4.3 summarizes demographic and environmental determinants for *S. mansoni* infection in the study area. The overall estimated mean population size was 3,358 inhabitants, and there were 1,011 households. On average, there were 6.5 inhabitants per household. The mean altitude was 339 m (standard error = 13 m) above mean sea level.

Rice cultivation was practiced in 71 (95%) communities. Thirty communities had a health facility in the village. ACT and praziquantel were available in 21 and 11 health facilities, respectively. Of note, all praziquantel stocks in the 11 health facilities were expired and also one-third (33%) of the ACT tablets in the 21 health facilities had passed their shelf life. There were 57 and 48 communities with permanent and seasonal stagnant water bodies, respectively. The corresponding values for rivers were 67 and 51.

Recreational and occupational risk-related behaviors for *S. mansoni* infection are shown in Table 4.4. Open defecation was practiced in all 75 communities and open surface water was used for washing in 48 communities and for bathing in 47 communities. Only 28 schools reported that open surface water was used for drinking. Among sanitation facilities, traditional pit latrines were the most common type (84%). Village authorities reported that the number of permanent rivers, streams, lakes, and ponds in the communities ranged from zero to 12 and that of seasonal water bodies ranged from zero to eight. Natural open freshwater bodies were predominantly used for washing and bathing. Well water was the most widely used type of water for drinking, washing, and bathing.

Table 4.3: Potential demographic, health system-related, and environmental risk factors for *Schistosoma mansoni* in the western part of Côte d'Ivoire

Variable	Mean	SE
No. of inhabitants/locality	3,357.9	409.2
No. of households/locality	1,010.6	291.1
No. of persons/household	6.5	0.6
Altitude (in meters)	338.9	12.5
	N	(%)
Main water contact-related activities		
Rice cultivation	71	94.7
Irrigated cultures	48	64
Fishing activities	54	72
Health system indicators		
Functional health center	30	40
Praziquantel availability	11	14.7
ACTs availability	21	28

Waterbodies			
	No permanent stagnant waterbodies (PSW)	18	24
	No. of PSW: 1 to 3	39	52
	No. of PSW: > 3	18	24
	No seasonal stagnant waterbodies (SSW)	27	36
	No. of SSW: 1 to 3	40	53.3
	No. of SSW: > 3	8	10.7
Rivers			
	No permanent streams or rivers (PR)	8	10.7
	No. of PR: 1 to 3	47	62.7
	No. of PR: >3	20	26.7
	No seasonal streams or rivers (SR)	24	32
	No. of SR: 1 to 3	42	56
	No. of SR: > 3	9	12

ACT = artemisinin-based combination therapy; PR = permanent rivers or streams; PSW = permanent stagnant water bodies; SE = standard error; SR = seasonal rivers or streams; SSW = seasonal stagnant water bodies.

Table 4.4: Potential risk-related behaviors of school-aged children that govern *Schistosoma mansoni* infection in the western part of Côte d'Ivoire

Variable	Practiced		Mean prominence
	n	(%)	
Drinking water sources			
Open surface water	28	37.3	0.78
Cistern water	50	66.7	1.06
Well water	73	97.3	2.83
Tap water	10	13.3	0.29
Water sources used for washing			
Open surface water	48	64	1.38
Cistern water	67	89.3	1.49
Well water	72	96	2.49
Tap water	8	10.7	0.25
Water sources used for bathing			
Open surface water	47	62.7	1.24
Cistern water	62	82.7	1.33
Well water	72	96	2.67
Tap water	9	12	0.27
Defecation behavior			
Open defecation	75	100	2.8
Pit latrine	63	84	1.33
Improved latrine	1	1.3	0.01
Toilet/WC	44	58.7	0.83

4.5. Discussion

Preventive chemotherapy with praziquantel is the current mainstay of schistosomiasis control, and efforts are underway to scale-up treatment coverage to reach the goal of globally controlling schistosomiasis by the year 2020. WHO recommends specific frequencies of praziquantel administration to school-aged children, as function of prevalence level, usually assessed by standardized parasitologic tests such as the Kato-Katz technique for *S. mansoni* diagnosis. To determine the best strategy of preventive chemotherapy with praziquantel to sustain the control of schistosomiasis mansoni in moderate endemicity settings (defined as prevalence in 13- to 14-year-old children ranging between 10% and 24%), a 4-year cluster randomized intervention trial is currently implemented in Côte d'Ivoire within the frame of a multi-country SCORE study (Assaré et al., 2014; Colley, 2014). Here, we report the baseline parasitologic situation and village characteristics before the onset of the trial and show the challenge of categorizing communities based on a rapid assessment procedure with a relatively small sample size (50 children) and an insensitive diagnostic method (Kato-Katz technique) (Utzing et al., 2015).

Examining single stool samples with duplicate Kato-Katz thick smears, we observed an overall *S. mansoni* prevalence of 15.8% in 13- to 14-year-old children at the eligibility survey. When 9- to 12-year-old children were examined with at least quadruplicate Kato-Katz thick smears at the baseline survey, the overall prevalence of *S. mansoni* was 22.1%. It follows that the overall prevalence of *S. mansoni* in school-aged children randomized into the 75 intervention schools in this large part of western Côte d'Ivoire can be considered as moderate according to WHO (10–49%) and SCORE (10–24%) prevalence thresholds. However, there were quite a number of schools in the baseline survey that had a prevalence above 24% compared with the eligibility survey (28 schools or 37.3% above the 24% prevalence threshold). Three of the schools actually had a prevalence of 50% and higher, and hence, must be considered as high-endemicity areas when using the more conservative WHO definition. On the other hand, seven schools (9.3%) showed a prevalence below 10% when comparing baseline with eligibility survey data.

The difference in the observed prevalence can be explained as follows. First, the children surveyed at baseline were slightly younger than those surveyed at the eligibility survey (mean age: 10.5 years versus 13.2 years). It is widely acknowledged that the prevalence and intensity of *Schistosoma* infection increase from early age, peaks around 8–15 years, and decrease again in adulthood (Woolhouse, 1998). Second, the probability to detect a

S. mansoni case with four or more Kato-Katz thick smears derived from two or three consecutive stool samples per individual is considerably higher than when only a single stool sample is examined with duplicate Kato-Katz thick smears. The effect of increased sampling effort on the diagnostic sensitivity of the Kato-Katz method has been documented before, and hence, it is strongly recommended to examine multiple stool samples over multiple days to obtain a reliable prevalence estimate of *S. mansoni* and other helminths, particularly in settings where infection intensities are low (Utzinger et al., 2001; Booth et al., 2003; Enk et al., 2008; Coulibaly et al., 2012; Sayasone et al., 2015). Third, our results confirm that schistosomiasis is a focal disease; indeed, the prevalence of infection at the unit of the school showed considerable variation from one school to another (Assaré et al., 2015). Focality of *S. mansoni* is often explained with special occupational or recreational risk behaviors, proximity to open freshwater bodies that serve as habitat for intermediate host snails, and access to, and use of, sanitation facilities (Utzinger et al., 2000; Sow et al., 2008; Odiere et al., 2012; Grimes et al., 2015; Walz et al., 2015). In our study, for example, boys showed a higher infection prevalence than girls. This finding is in accordance with previous studies from Côte d'Ivoire and other parts of the world (Utzinger et al., 2000; Raso et al., 2005; Reta and Erko, 2013; Yapi et al., 2014). The most likely explanation for a higher infection level in boys compared with girls is that boys are more actively exploring the environments of their settlements, including rivers and ponds, and hence, boys are more exposed to *S. mansoni* infection (Rudge et al., 2008).

Previous research conducted in the village of Fagnampléu, in Tonkpi region, reported that prevalences of hookworm, *A. lumbricoides*, and *T. trichiura* were 60.0%, 3.4%, and 2.2%, respectively (Keiser et al., 2002). Another study, which took place in 57 schools of the Man region, revealed prevalences of 30.5%, 2.2%, and 1.3% for hookworm, *A. lumbricoides*, and *T. trichiura* infection, respectively (Raso et al., 2005). In our study, the corresponding values were 0.9%, 1.4%, and 3.2%, respectively. These results indicate that the prevalences of *A. lumbricoides* and *T. trichiura* were low in the study area. The unexpectedly low hookworm infection rate may be explained by the applied Kato-Katz procedure. In this study, the clearing time of the Kato-Katz thick smears between preparation and reading varied from 1 hour to several weeks, mainly explained by the large scale of the study with small mobile teams collecting and preparing Kato-Katz thick smears in the field with laboratory analysis done later on. Therefore, most of the hookworm eggs were dissolved and led to an underestimation of the actual prevalence (Martin and Beaver, 1968).

At the level of demographic and environmental characteristics of the local communities, we found that rice farming, which has been shown to be a determinant of schistosomiasis (Fournet et al., 2004; Matthys et al., 2007; Yapi et al., 2005), is widely practiced and thus may represent a major source of exposure in the study area. The importance of contact with cercariae-infested water through washing and bathing, combined with widespread open defecation, is acknowledged for governing the transmission of intestinal schistosomiasis (Utzinger et al., 2000, Sow et al., 2008; Odogwu et al., 2006, Mohammed et al., 2015; Nalugwa et al., 2015). Among our study population, open surface water was predominantly used for washing and bathing. Moreover, while basic sanitation facilities (i.e., traditional pit latrines) were reported to exist in most of the communities (84%), open defecation was very common. Indeed, open defecation was practiced in all settlements, which might be a main reason for the fecal contamination of freshwater bodies.

What warrants close attention over the course of the interventions, however, is the access to (unexpired), and use of, praziquantel and ACTs in the health facilities of the study communities and a potential change in the socioeconomic status, and proportion of people using improved sanitation. For sustainable control of schistosomiasis, it is crucial to not only regularly treat school-aged children with praziquantel, but also promote latrine construction and use, coupled with hygiene education and behavior change efforts (Schmidlin et al., 2013), and to make praziquantel available at all health centers so that those in need can get treatment. Our data showed that the proportions of first graders (mean age: 6.5 years) with heavy infection were higher than among 9- to 12-year-old children (mean age: 10.5 years). This observation might indicate an upsurge in transmission over the last few years.

4.6. Conclusion

Our findings show that prevalence estimates differ considerably, which is also influenced by age, sex, and sampling efforts and which needs to be taken into account when planning schistosomiasis control and elimination. The baseline characteristics presented here at the onset of a multi-year SCORE study provide important information for the years to come in this cluster-randomized intervention trial, which will help to determine the best strategies to sustainably control schistosomiasis mansoni in moderate endemicity areas. In addition, the results of this survey represent an extensive evidence-base for the extent of intestinal schistosomiasis and potential transmission sources to be addressed by the ongoing national schistosomiasis (and soil-transmitted helminthiasis) control program in Côte d'Ivoire.

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5. Paper 4 - Sustaining control of schistosomiasis mansoni in western Côte d'Ivoire: results from a SCORE study, one year after initial praziquantel administration

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5.1. Abstract

Background: The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) has launched several large-scale trials to determine the best strategies for gaining and sustaining control of schistosomiasis and transitioning toward elimination. In Côte d’Ivoire, a 5-year cluster-randomized trial is being implemented in 75 schools to sustain the control of schistosomiasis mansoni. We report *Schistosoma mansoni* infection levels in children one year after the initial school-based treatment (SBT) with praziquantel and compare with baseline results to determine the effect of the intervention.

Methodology: The baseline cross-sectional survey was conducted in late 2011/early 2012 and the first follow-up in May 2013. Three consecutive stool samples were collected from 9- to 12-year-old children in 75 schools at baseline and 50 schools at follow-up. Stool samples were subjected to duplicate Kato-Katz thick smears. Directly observed treatment (DOT) coverage of the SBT was assessed and the prevalence and intensity of *S. mansoni* infection compared between baseline and follow-up.

Principal Findings: The *S. mansoni* prevalence in the 75 schools surveyed at baseline was 22.1% (95% confidence interval (CI): 19.5–24.4%). The DOT coverage was 84.2%. In the 50 schools surveyed at baseline and one year after treatment, the overall prevalence of *S. mansoni* infection decreased significantly from 19.7% (95% CI: 18.5–20.8%) to 12.8% (95% CI: 11.9–13.8%), while the arithmetic mean *S. mansoni* eggs per gram of stool (EPG) among infected children slightly increased from 92.2 EPG (95% CI: 79.2–105.3 EPG) to 109.3 EPG (95% CI: 82.7–135.9 EPG). In two of the 50 schools, the prevalence increased significantly, despite a DOT coverage of >75%.

Conclusions/Significance: One year after the initial SBT, the *S. mansoni* prevalence had decreased. Despite this positive trend, an increase was observed in some schools. Moreover, the infection intensity among *S. mansoni*-infected children was slightly higher at the 1-year follow-up compared to the baseline situation. Our results emphasize the heterogeneity of transmission dynamics and provide a benchmark for the future yearly follow-up surveys of this multi-year SCORE intervention study.

5.2. Author summary

Schistosomiasis is a parasitic worm disease that is widespread in sub-Saharan Africa. To better understand how to gain and sustain the control of schistosomiasis and how to eliminate this disease in different epidemiologic settings, the Schistosomiasis Consortium for

Operational Research and Evaluation (SCORE) has launched several multi-year studies that are being implemented in East and West Africa. This article highlights how the *Schistosoma mansoni* infection levels changed one year after an initial treatment with the antiworm drug praziquantel given to children aged 5–15 years in western Côte d’Ivoire. Infection and treatment data at school level were available from more than 4,600 children in 50 schools. One year after the treatment that had been received by more than 80% of the children, the overall *S. mansoni* prevalence decreased from 19.7% to 12.8%, while the intensity of infection among *S. mansoni*-positive children slightly increased. In several schools, the *S. mansoni* intensity and, particularly the prevalence, increased unexpectedly. Our findings show that the dynamics of schistosomiasis transmission varies from one village to another. It will be interesting to monitor changes over longer time periods as this SCORE study unfolds.

5.3. Introduction

Schistosomiasis is a neglected tropical disease that exerts a considerable public health problem in 78 tropical and subtropical countries (WHO, 2014). In 2013, it was estimated that schistosomiasis affected more than 250 million people worldwide with 90% of the reported cases concentrated in sub-Saharan Africa (WHO, 2015). Since the mid-1980s, the World Health Organization (WHO) emphasizes morbidity control using the drug praziquantel as the main pillar of the global strategy to fight schistosomiasis (WHO, 1985). Praziquantel is the drug of choice because it is efficacious against the adult stages of all *Schistosoma* species parasitizing humans, is inexpensive (the average cost to treat a school-aged child was US\$ 0.2 per treatment in 2013), and has a good safety profile (Bergquist, 2002; Doenhoff et al., 2002; Singer and de Castro, 2007; Zhang et al., 2010; Thétiot-Laurent et al., 2013). For morbidity control, praziquantel is being administered to at-risk populations without prior diagnosis, a strategy commonly known as ‘preventive chemotherapy’ (WHO, 2006a).

The recommended frequency of drug administration is based on the level of endemicity in a given study area. According to WHO, in areas with high schistosomiasis endemicity (prevalence $\geq 50\%$), all school-aged children and adult people at risk of infection should be treated annually (WHO, 2013). In areas with moderate endemicity (prevalence 10–50%), all school-aged children should be treated once every two years. In low endemic areas (prevalence $< 10\%$), school-aged children should be treated twice during their time in school; first at school entry and then again in their last year of schooling (WHO, 2006b; WHO, 2012). However, these prevalence thresholds are arbitrary. Hence, the Schistosomiasis Consortium

for Operational Research and Evaluation (SCORE) launched a series of studies to strengthen the evidence-base how best to gain and sustain the control of schistosomiasis, including cost considerations (Colley, 2014). Two 5-year cluster-randomized trials are being implemented in Côte d’Ivoire and Kenya (Samuels et al., 2012; Assaré et al., 2014). These trials are school-based with three treatment arms (25 schools per arm) and aim to assess whether annual school-based treatment (SBT) with praziquantel for four years (arm A), annual SBT in years 1 and 2, followed by “drug holidays” in years 3 and 4 (arm B), or SBT in years 1 and 3, spaced by “drug holidays” in years 2 and 4 (arm C) will substantially reduce the prevalence and intensity of *Schistosoma* infection and keep infection at low levels.

Here, we present the effect of the first SBT with praziquantel on *Schistosoma mansoni* infection among school-aged children in western Côte d’Ivoire, as revealed by a detailed follow-up survey conducted in May 2013, compared to baseline data collected from December 2011 to February 2012. Specifically, we determined changes in the prevalence and intensity of *S. mansoni* infections among children in the 50 schools that belong to treatment arms A and B, and discuss consequences for the ongoing cluster-randomized trial and, more generally, for schistosomiasis control interventions in Côte d’Ivoire and elsewhere.

5.4. Methods

5.4.1. Ethics statement

The study protocol was approved by the institutional research commissions of the Swiss Tropical and Public Health Institute (Basel, Switzerland) and the ‘Centre Suisse de Recherches Scientifiques en Côte d’Ivoire’ (CSRS; Abidjan, Côte d’Ivoire). Ethical approval was obtained from the ethics committees in Basel (reference no. EKBB 279/10) and the Ministry of Public Health in Côte d’Ivoire (reference no. 1994 MSHP/CNER).

At the onset of the study, regional directors of the education and health sectors, education inspectors, village authorities, local community members, and teachers were sensitized in detail about the objectives of the research project. Parents and guardians of study participants provided written informed consent for children to participate. After the baseline parasitologic survey, in the frame of the first SBT conducted in June 2012, school-aged children living in the catchment area of participating schools were offered treatment with praziquantel at a single oral dose of 40 mg/kg of body weight (WHO, 2002).

5.4.2. Study area and population

The baseline survey was carried out from December 2011 to February 2012, the SBT in June 2012, and the first follow-up survey was conducted in May 2013 in eligible schools located in four regions of western Côte d'Ivoire: Cavally, Guemon, Haut-Sassandra, and Tonkpi. Details of the study area and population surveyed have been described elsewhere (Assaré et al., 2014; Assaré et al., 2016). The Cavally and Sassandra rivers and their tributaries represent the major hydrographic features of the study area (Kouamé et al., 2007; Aregheore, 2009). Buyo, a hydroelectric dam built across the Sassandra River in 1981, formed a lake with an estimated surface area of 600 km² (Kouamé et al., 2006). In western Côte d'Ivoire, the sources of water are traditional wells, rain water, rivers, water supply dams, ponds, creeks, fountains, natural spring water, and tap water (Fürst et al., 2009). The main reasons for human water contact that might lead to schistosomiasis transmission are washing dishes, washing children, fetching water, fishing, swimming, farming, and playing (Acka et al., 2010). Despite the existence of latrines in numerous households, open defecation is commonly practiced (Matthys et al., 2007; Luginbühl, 2008; Acka et al., 2010).

5.4.3. Sample size

The aim of the SCORE sustaining schistosomiasis control study implemented in western Côte d'Ivoire is to determine the best strategy of preventive chemotherapy with praziquantel to sustain schistosomiasis mansoni control in moderate endemicity settings (Assaré et al., 2014; Assaré et al., 2016). For this purpose, the *S. mansoni* prevalence in n schools in three treatments arms is compared over a study period of four years. The prevalence of *S. mansoni* is determined by testing m children in those schools where there is subsequent treatment. The effect of the different treatment intervals on the *S. mansoni* prevalence will be estimated using the following logistic regression model: $\log (p_{ijt} / (1 - p_{ijt})) = \mu + \alpha_i + \beta_t + \gamma_{ik}$, where p_{ijt} denotes the prevalence of *S. mansoni* in school j receiving treatment i in year t , μ is an intercept term, α_i is the effect of treatment i , β_t is the effect of time t , and γ_{ik} is the time by treatment interaction. Generalized estimating equations have been used to fit these longitudinal data (Diggle et al., 2014). To take into account variation in the *S. mansoni* prevalence among schools, an overdispersion parameter ϕ was introduced into the model. When $\phi = 1$, all schools under the same treatment have identical prevalences, whereas ϕ increases with increasing variation of prevalence levels between villages.

The calculations revealed that studying 20 schools per arm and evaluating 100 individuals per school would result in minimum effect sizes of 5–12% with or without overdispersion. In order to increase the chance of detecting differences between the intervention arms, the number of intervention units was increased to 25 per arm. Consequently, a total of 75 schools with a *S. mansoni* prevalence of 10–24% according to results from an eligibility survey were randomized to one of the three treatment arms (Assaré et al., 2014). Treatment arm A receives SBT with praziquantel once every year for four years, arm B receives SBT in years 1 and 2, followed by “drug holidays” in years 3 and 4, and arm C receives SBT in years 1 and 3, alternated by “drug holidays” in years 2 and 4 (Assaré et al., 2014). Before administration of the first round of treatment, a detailed baseline survey was conducted.

5.4.4. Study procedures

Following the SCORE harmonization protocol, all 75 schools were included in the baseline parasitologic survey implemented in Côte d’Ivoire from December 2011 to February 2012. Children were treated with praziquantel in June 2012. Only the 50 schools belonging to treatment arms A and B were subjected to the first follow-up survey carried out in May 2013, while the 25 schools belonging to treatment arm C were not subjected to a follow-up survey, as they were on “drug holidays” in year 2.

Baseline and follow-up surveys pursued cross-sectional designs. Study procedures have been detailed elsewhere (Assaré et al., 2014; Assaré et al., 2016). In brief, in each of the selected schools, approximately 100 children were invited to participate in the study. Inclusion criteria were as follows: (i) age of children ranging between 9 and 12 years; (ii) presence of an informed consent sheet signed by parents/guardians; and (iii) children themselves assented orally. Over three consecutive days, children were invited to submit a portion of their own morning stool in a 125-ml plastic container. Every day, filled stool containers were collected by trained field enumerators and sent to the hospital laboratories in the towns of Biankouma, Danané, Douékoué, Guiglo, Kouibly, and Man for processing.

Stool specimens were subjected to the Kato-Katz method (Katz et al., 1972). In brief, duplicate Kato-Katz thick smears were prepared from a single stool sample, using 41.7 mg plastic templates. The thick smears were allowed to clear for at least 60 min and examined by experienced laboratory technicians under a light microscope at low magnification. Eggs from *S. mansoni*, and additionally from soil-transmitted helminth species, were counted and recorded for each species separately. For quality control, 10% of the slides were randomly

selected and re-read by a senior microscopist. In case of discrepancies, the results were discussed with the concerned microscopists and the slides re-read until agreement was reached (Speich et al., 2015).

5.4.5. *Praziquantel administration*

In June 2012, children aged 5–15 years enrolled in the 75 study schools and non-enrolled school-aged children living in the school catchment areas were offered free-of-charge treatment with praziquantel (40 mg/kg) using a dose pole according to WHO guidelines (WHO, 2002). Praziquantel was administered by trained teachers to children, following a directly observed treatment (DOT) approach. Children remained under medical observation and adverse events were recorded within 4 hours post-treatment. Treatment was led by the ‘Programme National de Lutte contre la Schistosomiase, les Géohelminthiases et la Filariose Lymphatique’ (PNL-SGF), and supported by staff from the ‘Programme National de Santé Scolaire et Universitaire’ (PNSSU), the CSRS, and the ‘Université Félix Houphouët-Boigny’. Praziquantel tablets were supplied by the Schistosomiasis Control Initiative (SCI; London, United Kingdom).

The overall number of school-aged children residing in each village was obtained by adding up the number of school-aged but non-school attending children as recorded by the community health workers and the number of children registered in school, as detailed by school teachers. Trained teachers administered praziquantel to children (those attending school, and the non-enrolled children) and recorded the number of treated children.

5.4.6. *Statistical analysis*

Baseline survey data were entered into Microsoft Excel (2010 Microsoft Corporation), while data from the first follow-up survey were directly entered into smartphones and then uploaded to a database maintained on a central server (Open Data Kit) in Atlanta, United States of America. Statistical analyses were performed with STATA version IC13.1 (Stata Corporation; College Station, United States of America). The final analysis included children aged 9–12 years who had at least four Kato-Katz thick smear readings at the parasitologic surveys done both at baseline and follow-up. To obtain individuals’ eggs per gram of feces (EPG), we divided the total *S. mansoni* egg counts from the multiple Kato-Katz slides per child by the total number of Kato-Katz thick smears and multiplied by a factor of 24. *S. mansoni*-positive individuals were stratified into three infection intensity categories: (i) light (1–99 EPG), (ii) moderate (100–399 EPG), and (iii) heavy (≥ 400 EPG) (WHO, 2002). Moreover, we

calculated *S. mansoni* prevalence and arithmetic mean (AM) EPG for positive individuals per school and treatment arm. With regard to soil-transmitted helminth infections that were also identified with the Kato- Katz technique, a child was considered positive if at least one egg of *Ascaris lumbricoides*, hookworm, or *Trichuris trichiura* was detected in one of the slides.

We employed a χ^2 test to assess a potential association between *S. mansoni* prevalence and age or sex. Reduction in the prevalence and intensity of *S. mansoni* infection per school was calculated using the following formulae (Montresor et al., 1998): prevalence reduction = [(prevalence at baseline—prevalence at first follow-up) / (prevalence at baseline)] X 100. Reduction in the intensity of infection = [(AM EPG at baseline—AM EPG at first follow-up) / (AM EPG at baseline)] X 100.

The treatment coverage rate was assessed by using the following formula: coverage of the mass drug administration (MDA) = [(number of school-aged children with DOT recorded by teachers) / (overall number of school-aged children registered in school and recorded by health workers)] X 100.

Geographic coordinates of each school were recorded using a hand-held global positioning system (GPS) receiver (Garmin Etrex 30; Olathe, United States of America). Arc Map 10.2.1 (Environmental Systems Research Institute Inc.; Redlands, United States of America) was used to generate maps of the changes of *S. mansoni* prevalence and intensity of infection (AM EPG) from baseline to follow-up.

5.5. Results

5.5.1. Operational results from baseline survey

The baseline survey was conducted in the 75 schools meeting eligibility criteria from December 2011 to February 2012, and 7,478 children were invited to participate (Fig 5.1). Among them, 168 pupils were excluded from further analyses, because their age was outside the 9–12 years range. Additionally, 299 children were excluded because they did not provide sufficient stool to prepare at least quadruplicate Kato-Katz thick smears. The final study population for analysis of the baseline survey consisted of 7,011 children. There were more boys (n = 4,173) than girls (n = 2,838). The mean age was 10.5 years. The number of children in treatment arms A, B, and C was 2,410 (34.4%), 2,348 (33.5%), and 2,253 (32.1%), respectively.

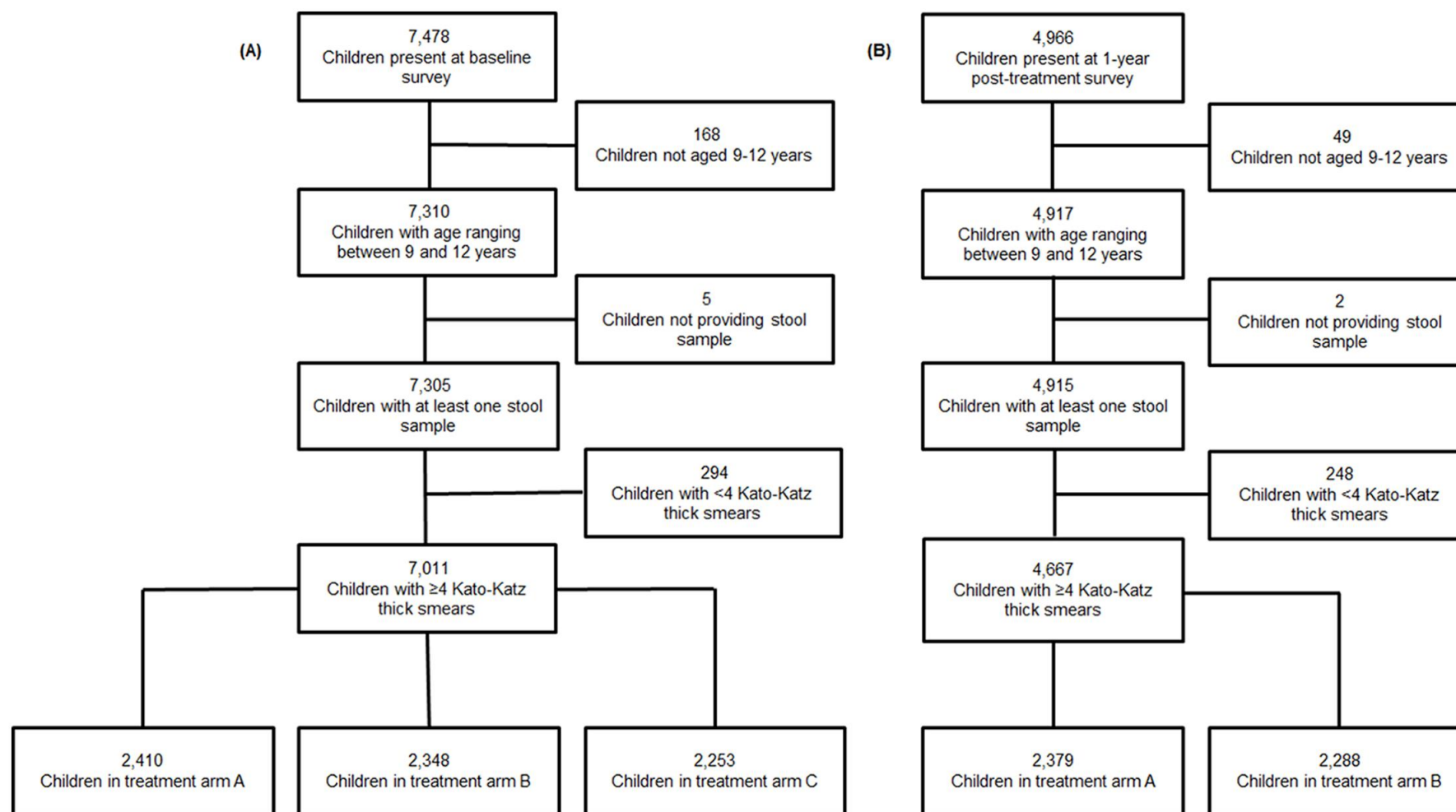


Figure 5.1: Study participation of schoolchildren at the baseline survey and one-year follow-up survey. The flowcharts show the study participation of 9- to 12-year-old schoolchildren at the baseline survey (A), which was conducted from December 2011 to February 2012, and the first follow-up survey (B), which was carried out one-year post-treatment in May 2013, in western Côte d’Ivoire

5.5.2. Operational results from first follow-up survey

In May 2013, 4,966 children from the 50 schools belonging to intervention arms A and B were invited to participate in the first follow-up survey. According to the SCORE harmonization protocol, children attending schools belonging to study arm C were not surveyed. Among the pupils attending schools included in arms A and B, who were invited to participate, 49 children had an age outside the 9–12 years range, and 250 children did not provide enough stool for at least quadruplicate Kato-Katz thick smears. Hence, results of 4,667 children were included for further statistical analyses. There were more boys ($n = 2,640$) than girls ($n = 2,027$). The children's mean age was 10.3 years. There were 2,379 children in treatment arm A and 2,288 in treatment arm B.

5.5.3. *S. mansoni* infection at baseline

At baseline, before the implementation of the first SBT with praziquantel, the examination of at least four Kato-Katz thick smears per child revealed an overall *S. mansoni* prevalence of 22.1% among the 75 schools surveyed. The prevalence at the unit of the school ranged from 1.0% to 54.0%. *S. mansoni* infection was significantly associated with age ($\chi^2 = 25.2$, $p < 0.001$), higher prevalence was predominantly observed among older children. The prevalence of *S. mansoni* was significantly higher among boys than girls (24.3% versus 18.7%; $\chi^2 = 29.9$, $p < 0.001$). The overall *S. mansoni* prevalence in treatment arms A, B, and C was 18.8% (95% CI: 17.2–20.3%), 20.5% (95% CI: 18.9–22.2%), and 27.2% (95% CI: 25.3–29.0%), respectively. With regard to the AM infection intensity, the respective values were 93.5 EPG (95% CI: 62.6–124.4 EPG), 96.2 EPG (95% CI: 74.5–117.9 EPG), and 88.1 EPG (95% CI: 71.5–104.7 EPG) (Table 1).

5.5.4. Changes of *S. mansoni* prevalence at the first follow-up survey

As summarized in Table 1, at the first follow-up survey, the overall *S. mansoni* prevalence in arms A and B showed a statistically significant decline from 19.7% (95% CI: 18.5–20.8%) at baseline to 12.8% (95% CI: 11.9–13.8%) at the 1-year follow-up. In arm A, a decrease from 18.8% (95% CI: 17.2–20.3%) to 11.2% (95% CI: 9.9–12.4%) was observed, corresponding to a reduction of 40.4%, while in arm B the prevalence declined from 20.5% (95% CI: 18.9–22.2%) to 14.5% (95% CI: 13.1–16.0%), a reduction of 29.3%.

Fig 5.2 indicates the dynamics of the *S. mansoni* prevalence from baseline to first follow-up survey on a school-by-school basis, stratified by treatment arm. Among the 25

Table 5.1: *S. mansoni* and soil-transmitted helminth infection prevalence at the baseline and follow-up surveys, stratified by treatment arm.

Arms	Baseline				One-year post-treatment				Change (%)
	Examined	Infected	Prevalence		Examined	Infected	Prevalence		
	N	N	(%)	(95% CI)	N	N	(%)	(95% CI)	
Arm A									
<i>S. mansoni</i>	2,410	453	18.8	(17.2-20.3)	2,379	266	11.2	(9.9-12.4)	-40.4
Hookworm	2,410	16	0.7	(0.3-1.0)	2,379	2	0.1	(0.0-0.2)	-85.7
<i>A. lumbricoides</i>	2,410	23	0.9	(0.6-1.3)	2,379	11	0.5	(0.2-0.7)	-44.4
<i>T. trichiura</i>	2,410	82	3.4	(2.7-4.1)	2,379	42	1.8	(1.2-2.3)	-47.1
Arm B									
<i>S. mansoni</i>	2,348	482	20.5	(18.9-22.2)	2,288	332	14.5	(13.1-16.0)	-29.3
Hookworm	2,348	24	1.0	(0.6-1.4)	2,288	2	0.1	(0.0-0.2)	-90.0
<i>A. lumbricoides</i>	2,348	12	0.5	(0.2-0.8)	2,288	10	0.4	(0.2-0.7)	-20.0
<i>T. trichiura</i>	2,348	75	3.2	(2.5-3.9)	2,288	39	1.7	(1.2-2.2)	-46.9
Arm C									
<i>S. mansoni</i>	2,253	612	27.2	(25.3-29.0)	NA				
Hookworm	2,253	55	2.4	(1.8-3.1)	NA				
<i>A. lumbricoides</i>	2,253	31	1.4	(0.9-1.9)	NA				
<i>T. trichiura</i>	2,253	64	2.8	(2.2-3.5)	NA				
Overall									
<i>S. mansoni</i>	7,011	1,547	22.1	(19.5-24.4)	4,667	598	12.8	(11.9-13.8)	-42.1
Hookworm	7,011	95	1.4	(1.1-1.6)	4,667	4	0.1	(0.0-0.2)	-92.9
<i>A. lumbricoides</i>	7,011	66	0.9	(0.7-1.2)	4,667	21	0.4	(0.3-0.6)	-55.6
<i>T. trichiura</i>	7,011	221	3.2	(2.7-3.6)	4,667	81	1.7	(1.4-2.1)	-46.9

Prevalence of *S. mansoni* and soil-transmitted helminth infections among 9- to 12-year-old schoolchildren in the schools belonging to treatment arms A and B, respectively, at the baseline survey, which was conducted from December 2011 to February 2012, and the first follow-up survey, which was carried out one-year post-treatment in May 2013, in western Côte d'Ivoire.

Arm A: schools receive praziquantel treatment annually for four years, Arm B: schools receive praziquantel treatment in the first two years of the study, followed by two years of “drug holiday”; Arm C: schools receive praziquantel treatment in the first and third year of the study and have “drug holidays” in the second and fourth year.

CI: confidence interval; NA: not assessed.

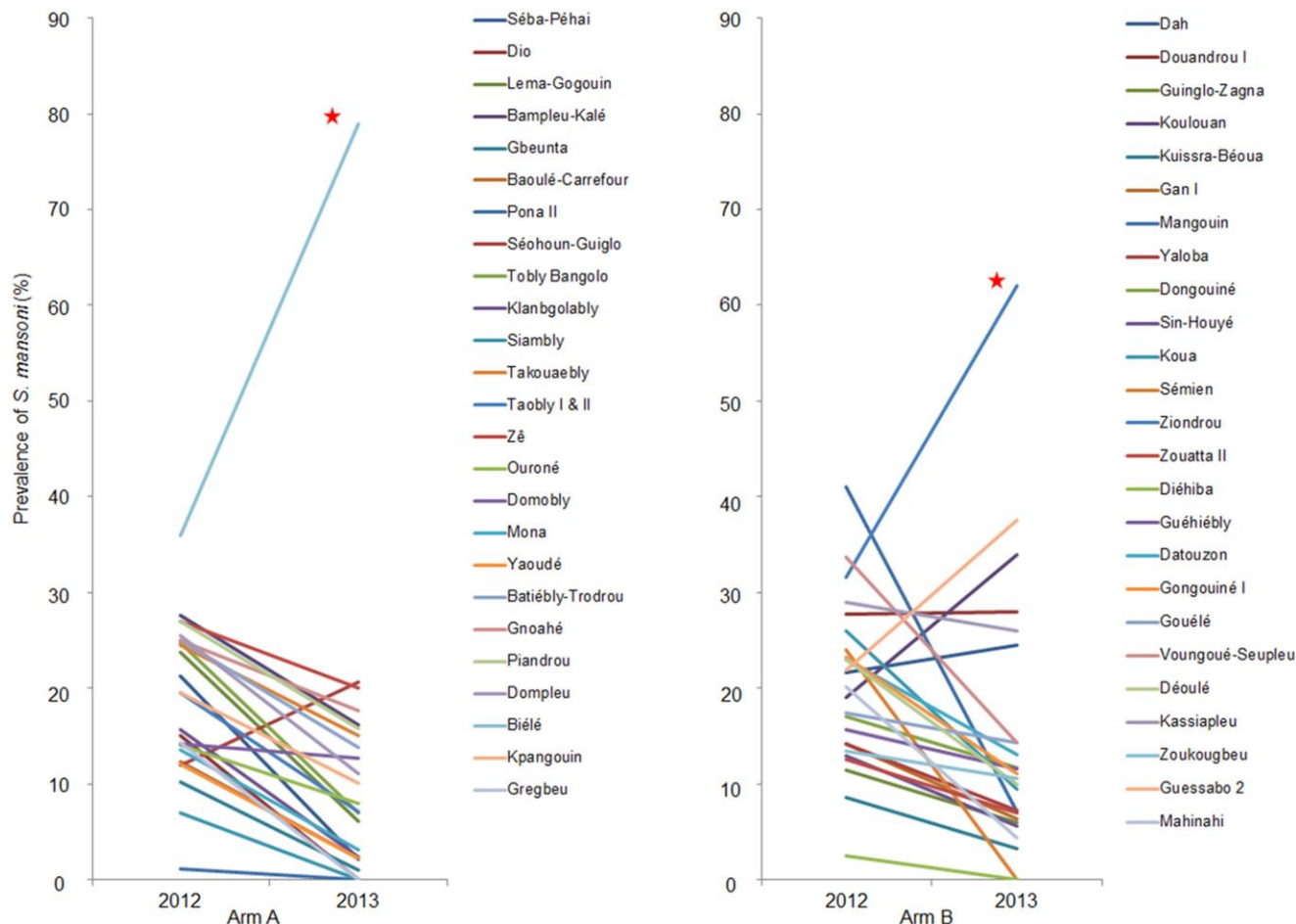


Figure 5.2: Dynamics of the *S. mansoni* prevalence in schools of treatment arms A and B. The graphs show the change of the *S. mansoni* prevalence from the baseline survey, which was conducted from December 2011 to February 2012, to the first follow-up survey, which was carried out one-year posttreatment in May 2013, in 9- to 12-year-old schoolchildren from 25 schools per treatment arm in western Côte d’Ivoire. Arm A: schools receive praziquantel treatment annually for four years, Arm B: schools receive praziquantel treatment the first two years of the study, followed by two years of “drug holiday”. Red star: *S. mansoni* prevalence increased significantly.

schools belonging to treatment arm A, the *S. mansoni* prevalence dropped in 23 schools (S1 Table). The most significant decreases occurred in Dio, Pona 2, Siambly, and Gregbeu, where at the 1-year follow-up, no eggs of *S. mansoni* were found in the stool of the children

examined. However, in Biélé, the *S. mansoni* prevalence increased significantly from 36.0% (95% CI: 26.4–45.6%) to 79.0% (95% CI: 70.9–87.1%), while a non-significant increase from 12.0% (95% CI: 5.5–18.5%) to 20.7% (95% CI: 12.0–29.4%) was observed in Séohoun-Guiglo.

In treatment arm B, the prevalence of *S. mansoni* decreased in 20 out of the 25 schools included (S1 Table). In two schools, the prevalence dropped prominently to zero from 24.0% in Semien and from 25.6% in Diehiba. A significant increase in the *S. mansoni* prevalence was observed in Ziondrou from 31.6% (95% CI: 22.0–41.1%) to 62.0% (95% CI: 52.3–71.7%). An increase in prevalence was also observed in Dah, Douandrou 1, Koulouan, and Guessabo 2, but without statistical significance.

Taken together, as shown in Fig 3A, among the 50 schools surveyed at the first follow-up, a reduction of the *S. mansoni* prevalence of 25% and above was observed in 39 schools (78.0%). In six schools, the changes ranged from -25% to +25%. An increase of 25% and above was recorded in five schools (10.0%). The increase in prevalence was observed mainly in the central part of Guemon region, eastern Tonkpi region, and western part of Haut-Sassandra region.

5.5.5. Changes of *S. mansoni* infection intensity at the first follow-up survey

The overall *S. mansoni* AM EPG in arms A and B increased from 94.9 EPG (95% CI: 76.2–113.6 EPG) at baseline to 109.3 EPG (95% CI: 82.7–135.9 EPG) at the 1-year follow-up survey. However, this increase was not statistically significant. As shown in Table 2, in arm A, an increase from 93.5 EPG (95% CI: 62.6–124.4 EPG) to 123.7 EPG (95% CI: 70.7–176.7 EPG) was observed, corresponding to an increase of 32.3%, while in arm B the AM EPG at baseline (96.2 EPG, 95% CI: 74.5–117.9 EPG) and the 1-year follow-up (97.8 EPG, 95% CI: 75.5–120.0 EPG) remained basically the same. The proportion of children with heavy infections (≥ 400 EPG) increased from 4.9% to 6.3%.

Fig 5.4 displays the changes of the *S. mansoni* AM EPG in all the schools of treatment arms A and B from baseline to the first follow-up. In arm A, the *S. mansoni* AM EPG decreased in 16 (64.0%) out of the 25 surveyed schools (S1 Table). However, a statistically significant decrease in AM EPG from 33.0 EPG (95% CI: 13.9–52.0 EPG) to 5.5 EPG (95% CI: 3.8–7.2 EPG) was observed in only one school; Tobly Bangolo. Increases in *S. mansoni* AM EPG were observed in nine schools. However, the increase lacked statistical significance

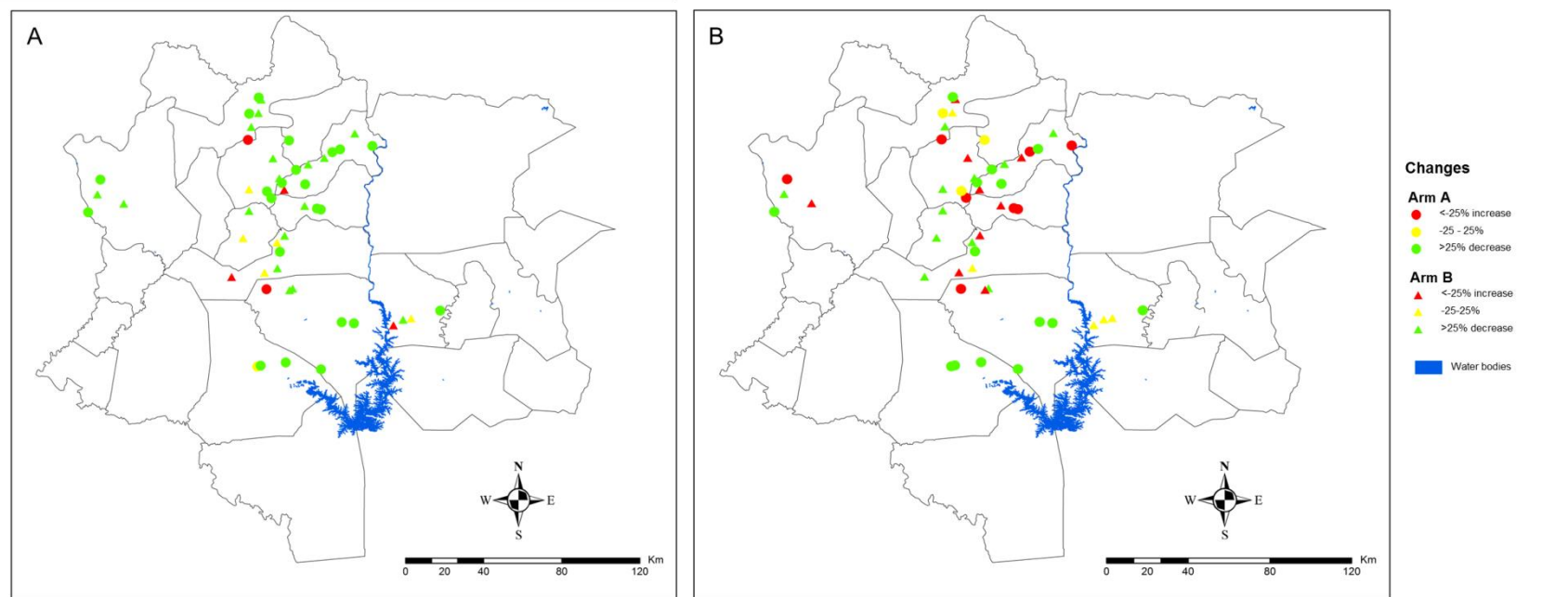


Figure 5.3: *S. mansoni* prevalence and infection intensity (AM EPG) at the baseline and follow-up survey. The maps show the spatial distribution of the changes in the *S. mansoni* prevalence and in the infection intensity expressed as arithmetic mean eggs per gram of feces (AM EPG) between the baseline survey (A), which was conducted from December 2011 to February 2012, and the first follow-up survey (B), which was carried out one-year post-treatment in May 2013, in western Côte d'Ivoire. Arm A: schools receive praziquantel treatment annually for four years, Arm B: schools receive praziquantel treatment the first two years of the study, followed by two years of “drug holiday”.

Table 5.2: *S. mansoni* infection intensity in the schools belonging to treatment arms A, B, and C.

Arm	Baseline						One-year post-MDA						Change
	No. examined	No. positive	Arithmetic mean EPG (95% CI)	Light (%)	Moderate (%)	Heavy (%)	No. examined	No. positive	Arithmetic mean EPG (95% CI)	Light (%)	Moderate (%)	Heavy (%)	
Arm A	2,410	453	93.5 (62.6-124.4)	85.9	9.5	4.6	2,379	266	123.7 (70.7-176.7)	79.3	13.5	7.2	-32.2
Arm B	2,348	482	96.2 (74.5-117.9)	81.1	12.9	6.0	2,288	332	97.8 (75.5-120.0)	75.6	18.7	5.7	-1.7
Arm C	2,253	612	88.1 (71.5-104.7)	77.1	18.8	4.1	NA	NA	NA	NA	NA	NA	
Overall	7,011	1,547	92.2 (79.2-105.3)	80.9	14.2	4.9	4,667	598	109.3 (82.7-135.9)	77.3	16.4	6.3	-18.5

S. mansoni arithmetic mean intensity of infection among 9- to 12-year-old schoolchildren in the schools belonging to treatment arms A, B, and C, respectively, as determined at the baseline survey, which was conducted from December 2011 to February 2012, and the first follow-up survey, which was carried out one-year post-treatment in May 2013, in western Côte d’Ivoire.

Arm A: schools receive praziquantel treatment annually for four years, Arm B: schools receive praziquantel treatment in the first two years of the study, followed by two years of drug holiday; Arm C: schools receive praziquantel treatment in the first and third year of the study and have “drug holidays” in the second and fourth year.

NA: not assessed; CI: confidence interval; EPG: eggs per gram of feces.

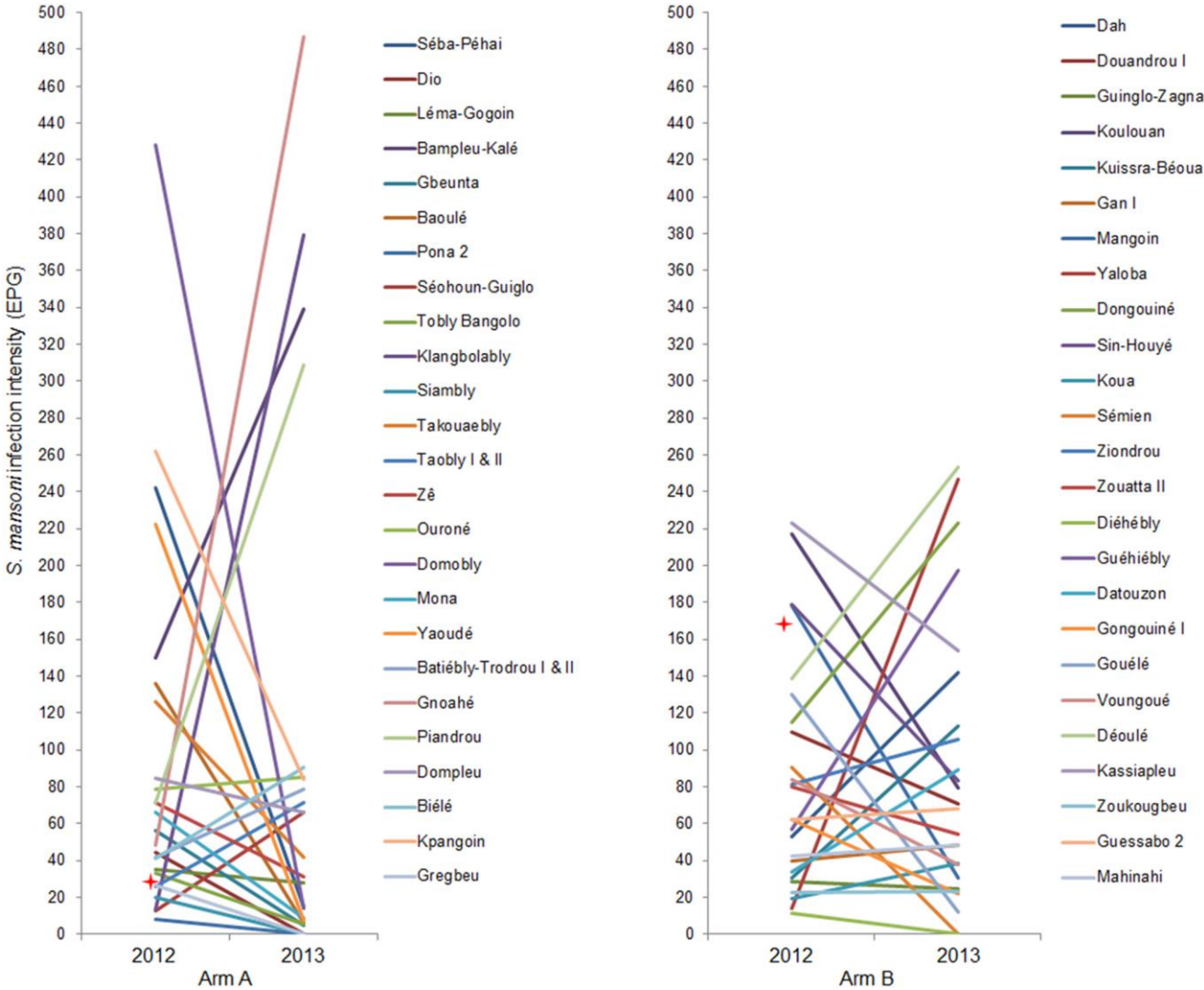


Figure 5.4: Dynamics of the *S. mansoni* infection intensity in schools of treatment arms A and B. The graphs show the change of the *S. mansoni* infection intensity expressed as change in arithmetic mean eggs per gram of feces (AM EPG) from the baseline survey, which was conducted from December 2011 to February 2012, to the first follow-up survey, which was carried out one-year post-treatment in May 2013, in 9- to 12-year-old schoolchildren from 25 schools per treatment arm in western Côte d’Ivoire. Arm A: schools receive praziquantel treatment annually for four years, Arm B: schools receive praziquantel treatment the first two years of the study, followed by two years of “drug holiday”. Red star: *S. mansoni* infection intensity decreased significantly.

in all schools. In treatment arm A, the proportion of children with moderate (100–399 EPG) and heavy infections (≥ 400 EPG) increased from 9.5% to 13.5% and from 4.6% to 7.2%, respectively.

In arm B, a decrease of the *S. mansoni* infection intensity was observed in 13 (52.0%) out of the 25 schools (S1 Table). With the exception of one school, this decrease was not statistically significant. The AM EPG decreased significantly in Mangouin school from 178.0 EPG (95% CI: 77.7–278.3 EPG) to 30.4 EPG (95% CI: 4.2–56.6 EPG). In the remaining 12 schools, the AM EPG increased, but these increases lacked statistical significance. The proportion of children with moderate and heavy infection intensities increased from 12.9% to 18.7%, while the proportion of heavy infections decreased slightly from 6.0% to 5.7%.

Fig 3B shows the spatial distribution of *S. mansoni* AM EPG reduction after the intervention in the study area. The AM EPG decreased by at least 25% in 25 schools (50.0%). In eight schools (16.0%), the change varied from -25% to +25%. The AM EPG increased by 25% and more in 17 schools (34.0%). An increase of *S. mansoni* infection intensity by 25% and more was only focally observed; in Tonkpi region and central Guemon region.

5.5.6. Coverage of SBT

During the SBT carried out in June 2012, the estimated number of the school-aged population in the study area was 31,832 children. Among them, 26,804 swallowed praziquantel tablets at the SBT, resulting in an overall DOT coverage of 84.2%. Stratified by treatment arm, we found a DOT coverage of 79.2% (range: 31.9–97.9%) for arm A, 84.8% (range: 61.5–98.5%) for arm B, and 88.4% (range: 75.1–98.9%) for arm C.

The individual DOT coverage rates achieved in the 75 villages are shown in S2 Table. A coverage of 75% and above was achieved in 57 schools (76.0%), while a coverage of less than 75% was reported in the remaining 18 schools. Yaoudé (in arm A) reported a coverage below 50%. The DOT coverage was not significantly correlated with changing levels of *S. mansoni* prevalence (Spearman $\rho = -0.11$; $p = 0.43$), while it was significantly correlated with AM EPG (Spearman $\rho = 0.32$; $p = 0.02$) (Fig 5.5).

5.6. Discussion

Preventive chemotherapy with praziquantel is the backbone of the global strategy against schistosomiasis and other helminthiases (WHO, 2006b; Webster et al., 2014). Our findings show that one year after an initial treatment with praziquantel in 50 schools of western Côte

d'Ivoire that met inclusion criteria of a SCORE harmonization protocol (prevalence ranging between 10% and 24%) (Assaré et al., 2014), the overall *S. mansoni* prevalence was reduced from 19.7% to 12.8%, while there was no significant change in the overall AM EPG. The overall DOT coverage in the study area was 84.2%; hence, above the 75% coverage recommended by WHO (WHO, 2002). At school level, the picture on the impact of the SBT was less clear cut. Decreases in prevalence and infection intensity were observed in some schools and increases in others. Among the six schools that showed higher prevalences of *S. mansoni* at the 1-year follow-up compared with baseline, in only one school, the treatment coverage was <75%. The changes in the AM EPG level were significantly correlated with the coverage rate.

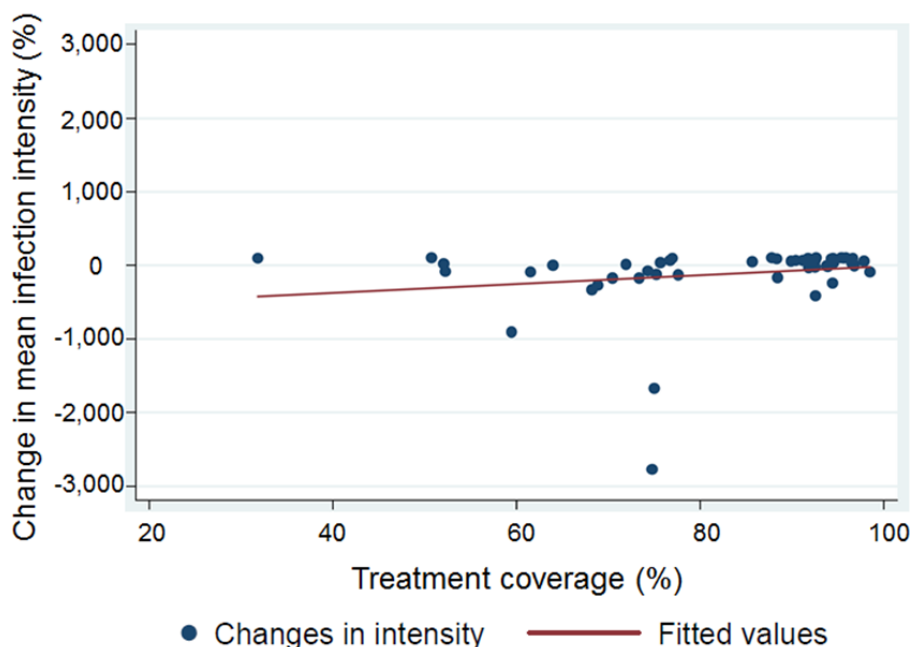


Figure 5.5: Correlation between coverage rate and the changes in the *S. mansoni* infection intensity. Scatter plot illustrating the correlation between the coverage rates achieved in a directly observed school-based treatment round implemented in 50 schools in western Côte d'Ivoire in June 2012, and the % changes in the *S. mansoni* arithmetic mean infection intensity observed between the baseline survey, which was conducted from December 2011 to February 2012, and the first follow-up survey, which was carried out one year post-treatment in May 2013, in 9- to 12-year-old schoolchildren.

The overall reduction of the *S. mansoni* prevalence in the first year of this SCORE project (35.0%) is in line with studies assessing the *S. mansoni* prevalence 12 months post-MDA in central Sudan and Uganda, where reductions of *S. mansoni* prevalence of 36.7% and

39.5% were observed, respectively (Zhang et al., 2007; Ahmed et al., 2012). The treatment coverage in these two studies was reported to be 100% and 79.2%, respectively (Kabatereine et al., 2006; Ahmed et al., 2012). In the Sudan study, treatment of children with praziquantel was conducted by trained nurses and medical officers, while in Uganda, the treatment was carried out by trained teachers and community drug distributors (Kabatereine et al., 2006; Ahmed et al., 2012). A survey conducted 6 months after praziquantel treatment in Sierra Leone where the overall treatment coverage was 94.0% found a reduction of the *S. mansoni* prevalence of 44.6% (Hodges et al., 2012). Another study carried out in Sierra Leone reported an even higher reduction in the *S. mansoni* prevalence of 67.2%, as determined three years after three rounds of praziquantel administration (Sesay et al., 2014). In contrast, studies conducted in Zambia and Kenya showed that 2 years after the withdrawal of praziquantel treatment led to an increase of *S. mansoni* prevalence (Sukwa et al., 1988; Masaku et al., 2015). It is important to note that these studies showed that the impact of MDA on the *S. mansoni* prevalence varied depending on the infection status in a given area, and the frequency and number of treatment rounds. Repeated treatments over short time periods can lead to a high reduction in *S. mansoni* prevalence compared to longer treatment intervals. Similar baseline *S. mansoni* prevalences were observed in two preceding studies in Sierra Leone and Uganda (49% and 42%, respectively), but the decrease in *S. mansoni* prevalence was lower in Uganda, where the intensity of infection, and thus the level of transmission, was higher. A plausible explanation of this observation arises from rapid re-infection, which is related to the force of infection, and which is likely higher where *S. mansoni* transmission is intense. Indeed, the level of schistosomiasis transmission, which is governed by various factors, such as local environmental determinants, climate, water contact patterns, intermediate host snail distribution, and ecology, may affect the impact of MDA (Zein, 1989; Ndyomugenyi and Minjas, 2001; Gazzinelli et al., 2006; Stothard et al., 2009b). When interpreting these results, one has to bear in mind, however, that the prevalence of *S. mansoni* was determined by an insensitive diagnostic approach; single stool samples subjected by single (Uganda) or duplicate Kato-Katz thick smears (Sierra Leone). Hence, the diagnostic approach was less rigorous than in the current study in Côte d'Ivoire, where only those children who had at least quadruplicate Kato-Katz thick smears examined before and after treatment were included in the final analysis.

In our study, in the schools Biélé and Ziondrou, the *S. mansoni* prevalence had significantly increased one year after SBT with levels in excess of 60%. Since the DOT

coverage in both schools was high (75.2% in Biélé and 91.9% in Ziondrou), we assume that there are major transmission hotspots in the area, where children become rapidly re-infected. Re-emergence of *S. mansoni* and *S. haematobium* after treatment in high-endemicity areas has previously been reported from other studies in Côte d'Ivoire and Niger (N'Goran et al., 2001; Garba et al., 2013). One explanation might be migration of people, including those infected with *S. mansoni* or *S. haematobium*, into treated villages. A considerable population movement has, for example, been observed in Côte d'Ivoire due to socio-political unrest in 2011 (Bonfoh et al., 2011), hence at the start of our study. A lack of access to safe water, sanitation, and hygiene (WASH) might also be the reason for rapid reinfection. Noteworthy, when interviewing the local village leaders, they reported that people in the area frequently use well water for washing and bathing, while ponds and rivers serve as the main natural water contact sites. While some houses have latrines, many people still practice open defecation. Another explanation of the increase in *S. mansoni* prevalence might be the target population of the treatment strategy. The present study focused on school-aged children. Preschool-aged children and adults also harbor *Schistosoma* worms, and hence, they act as reservoir of transmission source of re-infections (Masaku et al., 2015). Yet, there are other local conditions that might foster *S. mansoni* transmission in Biélé and Ziondrou that warrant further investigation. For example, one might want to assess the frequency and duration of water contact in children and associated re-infection patterns, and the transmission force caused by intermediate host snails populating waterbodies located in close proximity to the surveyed schools. It will be important to assess in future surveys whether individuals had indeed received praziquantel in the past treatment round, or whether they were immigrating from other areas after the last survey, or had traveled to highly endemic areas over the past year. Ideally, the reinfection pattern would be determined by following a cohort of children, including immunological markers of the individuals that might favor or delay reinfection, and molecular markers of the infecting parasites.

An increase of *S. mansoni* infection within the frame of ongoing treatment programs has also been observed elsewhere. In Senegal, for example, an elevated *S. mansoni* prevalence was found 10 months after praziquantel administration (Ernould et al., 1999). More recently, in Ségou district in Mali, the national control program had revealed an increase of the *S. mansoni* prevalence after four rounds of MDA in 7- to 14-year-old children (Landouré et al., 2012). It has been assumed that these increases of *S. mansoni* infections after praziquantel treatment might be explained by partial resistance to praziquantel, the acquisition of new

infection, and high force of transmission (Kabatereine et al., 1999; Stothard et al., 2009a; Wang et al., 2012).

Taken together, our data show that SBT resulted in marked decreases of *S. mansoni* prevalence, but the intensity of infection among infected children did not change significantly. Hence, with a single treatment round, the force of transmission in terms of egg excretion in the school-aged population has not been changed in most of our study schools. Monitoring the impact of multiple treatment rounds and “drug holidays” over the next years will provide stronger evidence of what multiple SBT rounds can achieve (Assaré et al., 2014; Colley, 2014).

Clearly, sustainable control and eventual elimination of schistosomiasis requires multiple intervention packages, such as preventive chemotherapy (perhaps extended to all age groups), intensified case management, control of intermediate host snails, provision of WASH, and setting-specific information, education, and communication (IEC) (Utzing et al., 2003; Lo et al., 2015; Wang et al., 2009). In Côte d’Ivoire, the control of schistosomiasis at a national scale is still at an early stage. Indeed, the PNL-SGF was only launched shortly before this SCORE project. For the success and sustainability of schistosomiasis control in Côte d’Ivoire—and elsewhere in sub-Saharan Africa—it will be important that, in addition to preventive chemotherapy, other control measures are considered and implemented (Utzing et al., 2003; Singer and de Castro, 2007; Utzing et al., 2009; Zhang et al., 2010).

5.7. Conclusion

The present study showed that one year after SBT with praziquantel, the overall prevalence of *S. mansoni* infection had decreased significantly. However, in certain hotspot schools, the *S. mansoni* prevalence had increased unexpectedly. The infection intensity among *S. mansoni* infected children was similar at the 1-year follow-up. These results demonstrated that the dynamic of schistosomiasis in the study areas is heterogeneous and that a single round of treatment is insufficient to have a lasting effect. It will be important to monitor the dynamic of schistosomiasis over the course of this SCORE study, in order to deepen our understanding of the dynamics of schistosomiasis transmission in a moderately endemic setting.

5.8. Acknowledgments

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5.9. Supporting information

S1 Table. Treatment coverage, and changes in *S. mansoni* prevalence and intensity of infection in 50 schools in western Côte d’Ivoire from 2012 to 2013.

(XLSX)

S2 Table. Praziquantel coverage of the school-based treatment conducted in 75 schools in western Côte d’Ivoire in June 2012, stratified by intervention arm.

(DOCX)

S1 Translation. Translation of abstract into French. (DOCX)

5.10. References

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6. Discussion

The present Ph.D. thesis is embedded in a project facilitated by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) that is funded by the Bill & Belinda Gates Foundation (Colley, 2014). The focus on the present work is epidemiology, spatial distribution and control of *S. mansoni* in four regions of western Côte d’Ivoire. In the first step, we contributed to the development and open-access publication of a study protocol for the implementation and monitoring of schistosomiasis mansoni control in areas with moderate endemicity (prevalence of the infection at the beginning of the study was ranging between 10% and 24%). The protocol was initially developed by a group of schistosomiasis experts from America, Europe and Africa. The study is a 4-year cluster-randomised controlled trial with three treatment arms, each arm including 25 schools (Assaré et al., 2014). In a second step, we mapped and predicted the spatial distribution of *S. mansoni* in the western part of Côte d’Ivoire. This piece of work was facilitated through the initial eligibility survey as part of the aforementioned cluster-randomised trial. We screened more than 250 schools, usually surveying 50 children per school and used Bayesian based statistics (Assaré et al., 2015). The risk map generated for *S. mansoni* in four regions of western Côte d’Ivoire already proved useful for the national schistosomiasis control programme for spatial targeting of preventive chemotherapy and other control interventions, in those schools that were not otherwise included in any ongoing trial. Thirdly, we determined the social-ecological baseline characteristics of local communities at the onset of our randomised controlled trial to sustain schistosomiasis mansoni control (Assaré et al., 2016a). This work allowed to assess the effect the sampling effort and the performance of the Kato-Katz technique and to determining *S. mansoni* infection level in our study area in the western part of Côte d’Ivoire. In the fourth step of our work we assessed the impact of the initial treatment round using single doses of praziquantel targeting all school-aged children for the prevalence and intensity of *S. mansoni* infection among 9 to 12 year-old children in western Côte d’Ivoire one year after the intervention. Moreover, we assessed the dynamics in the prevalence and intensity of *S. mansoni* infection from baseline to the one-year post-treatment follow-up.

Table 6.1 summarises how the current Ph.D. thesis contributes to innovation, validation and application, that represent some of the core concepts of the Swiss TPH. The study protocol and the results of the cross-sectional parasitological and questionnaire surveys, including a cluster-randomised controlled trial carried out in the frame of this Ph.D. thesis in four regions of western Côte d’Ivoire will be summarised and discussed in the following sections. Gaps,

future research needs and implication for sustainable control of schistosomiasis mansoni will be highlighted. The results of this thesis will be relevant for the national schistosomiasis control programme in Côte d'Ivoire and control programmes elsewhere in countries where schistosomiasis remains endemic.

Table 6.1: Contribution of the individuals chapters of this Ph.D. thesis to the innovation, validation and application nexus of Swiss TPH.

Chapter	Title	Innovation	Validation	Application
2	Sustaining control of schistosomiasis mansoni in moderate endemicity areas in western Côte d'Ivoire: a SCORE study protocol	Writing up the study protocol on determining the best strategy of MDA with praziquantel to sustain the control of <i>S. mansoni</i> in moderate endemicity areas in western Côte d'Ivoire for peer-reviewed literature	Focal distribution of <i>S. mansoni</i> confirmed for four regions of western Côte d'Ivoire	
3	The spatial distribution of <i>S. mansoni</i> infection in four regions of western Côte d'Ivoire	Risk factors for schistosomiasis mansoni identified and implications for the disease control discussed and disseminated to control managers		Risk map for schistosomiasis mansoni for in western Côte d'Ivoire used for spatial targeting of prevalence chemotherapy
4	Sustaining control of schistosomiasis mansoni in western Côte d'Ivoire: baseline findings before the implementation of a randomised trial	Baseline parasitological situation and social-ecological characteristics of local communities in western Côte d'Ivoire are determined Fragility of the classification of communities based on WHO criteria is demonstrated	Effect of sampling effort on the sensitivity of Kato-Katz technique confirmed	
5	Sustaining control of schistosomiasis mansoni in western Côte d'Ivoire: a SCORE study with results one year after initial praziquantel administration	Effects of a school-based MDA with praziquantel at regional scale on schistosomiasis are assessed for the first time in Côte d'Ivoire	The result of one year post-MDA underscored the need for an integrated approach for sustainable control schistosomiasis	The dynamic of <i>S. mansoni</i> prevalence and intensity of infection are determined and implication for schistosomiasis control discussed

6.1. Epidemiology of schistosomiasis mansoni in western Côte d'Ivoire

In western Côte d'Ivoire, *S. mansoni* is the predominant schistosome species. Since the 1970s, several research projects and control interventions have been implemented in this part of the country (Roux et al., 1974; Doumenge et al., 1987; Utzinger et al., 2000b; Raso et al., 2004a; Tchuem Tchuenté and N'Goran, 2009). Most of these preceding studies were implemented in the towns of Danané and Man and surrounding villages belonging to the Tonkpi region. Schistosomiasis is characterised by a focal distribution (Lengeler et al., 2002) hence the first step of any schistosomiasis control programme is an appraisal of the level of schistosomiasis endemicity in the area under study, in order to identify communities at risk for subsequent interventions. For the SCORE study presented here, we pursued a large-scale eligibility survey in four regions of western Côte d'Ivoire that governed a selection of target villages for a 4-year cluster-randomised controlled trial.

The identification of schistosomiasis prevalence at the community level on a large scale is a costly endeavour (Kurowski et al., 2007). Hence, rapid and inexpensive methods such as self-reported blood in urine (for *S. haematobium*) and self-reported blood in stool or bloody diarrhoea (for *S. mansoni*), and lot quality assurance sampling (LQAS) have been used to assess schistosomiasis endemicity of communities selected for any intervention trial (N'Goran et al., 1998; Utzinger et al., 2000b; Lengeler et al., 2002; Brooker et al., 2005; Krauth et al., 2015). It is widely acknowledged that school questionnaires are an effective and inexpensive tool to identify high-risk communities for *S. haematobium* (Lengeler et al., 2002). In contrast, for identification of communities at high-risk of *S. mansoni*, self-reported questionnaires only show moderate sensitivity and specificity, compared with standard parasitological surveys using Kato-Katz as diagnostic approach (Lengeler et al., 2002; Yang et al., 2015). According to WHO guidelines, the identification of *S. mansoni* prevalence should be based on a sample size of about 50 individuals (Montresor et al., 1998). During the eligibility surveys, we used the LQAS with 50 individuals per schools to determine 75 villages with a *S. mansoni* prevalence ranging between 10% and 24% (Assaré et al., 2014). Several epidemiological studies have shown that LQAS is the most rapid and cost-effective screening strategy to classify communities based on the disease endemicity level, particularly in low- and middle-income countries where human and financial resources are scarce (Brooker et al., 2005; Pezzoli and Kim, 2013).

Our large eligibility survey confirmed that western Côte d'Ivoire is highly endemic for *S. mansoni*. Indeed, the majority of schools (59.5%) surveyed had a *S. mansoni* prevalence

above 24% (Assaré et al., 2014). These high-risk schools were predominantly observed in the Tonpki region, while moderate *S. mansoni* prevalence schools were mostly found in the Gomon and Cavally regions (Assaré et al., 2015). Our baseline study showed that the categorisation of communities based on *S. mansoni* prevalence, determined by eligibility survey using a rapid appraisal approach, is fragile. Indeed, 28 of the schools that were determined to be of moderate endemicity in the eligibility survey showed a prevalence in excess of 24% during the baseline survey, while another 7 schools showed a prevalence below 10%. These patterns could be explained by the diagnostic strategy that was implemented; at eligibility, only one stool sample was collected, while at baseline multiple Kato-Katz thick smears were examined (at least four slides). In contrast, the lower observed infection prevalence in some locations might be related to the age or sex of study participants. The present study showed that *S. mansoni* prevalence increases with age and the prevalence of the disease being higher among boys compared with girls (Assaré et al., 2016a). The fragility of the categorisation of the community based on WHO thresholds as shown in our study calls for a more adequate tool for better categorising communities.

As expected, we found that the *S. mansoni* prevalence and intensity of infection were higher among 9- to 12 year-old children compared with first-graders. However, heavy infection intensities were predominantly observed in first-graders. This finding might suggest that transmission occurred in recent years, probably during the last decade of socio-political crisis (Tchuem Tchuente and N'Goran, 2009; Bonfoh et al., 2011).

6.2. Risk factors for schistosomiasis mansoni

Schistosomiasis is a water-borne disease that affects more than 250 million people, predominantly in sub-Saharan Africa (Hotez et al., 2014; WHO, 2015). Schistosomiasis is characterised by a micro-geographical heterogeneity (Cook and Zumla, 2009; Meurs et al., 2013; Assaré et al., 2014; Assaré et al., 2016) that is strongly associated with the distribution of intermediate host snails. The risk of humans to become infected with schistosomes depends on environmental, climatic and anthropogenic factors, affecting the distribution of schistosomiasis (Walz et al., 2015). These risk factors can be used to predict the distribution of the disease. Current epidemiological studies in the assessment of *S. mansoni* distribution reported that GIS and remote sensing are useful means for identification of risk factors for schistosomiasis. For example, it was reported that climatic features such as rainfall and LST, and environmental factors such as NDVI, altitude and large water bodies were the main

factors explaining the heterogeneity of schistosomiasis distribution at continental, national and sub-national levels (Chammartin et al., 2013; Stensgaard et al., 2013; Chammartin et al., 2014; Assaré et al., 2015b; Lai et al., 2015). In western Côte d'Ivoire, since 2005, remote sensing and GIS-based spatial analysis were conducted in this part of the country to map and predict the distribution of the disease (Raso et al., 2005; Beck-Worner et al., 2007). However, the studies were restricted to the town of Man and surrounding villages (within a diameter of approximately 30 km, in the Tonpki region). We have now generated a predictive risk map for schistosomiasis mansoni for four regions of western Côte d'Ivoire. Questionnaire-based methods have been successfully implemented to identify schistosomiasis mansoni associated risk factors at micro-geographical scale (Barreto, 1993; Bethony et al., 2001; Raso et al., 2005; Matthys et al., 2007). For our study we therefore used remote sensing and GIS coupled with Bayesian geostatistical methods to identify risk factors at a macro-geographical scale (i.e. at regional level) and questionnaire-based approach to determine potential risk factors at micro-geographical scale (i.e. at community level). Thus, the present study determined schistosomiasis risk factors at both the macro- and the micro-geographical scales. Importantly, the risk map for *S. mansoni* for the four regions of western Côte d'Ivoire has already been used by the national schistosomiasis control programme for spatial targeting of control interventions (Assaré et al., 2015).

On the macro-geographical scale, our results showed that environmental (i.e. altitude), demographic (i.e. sex and age) and climatic factors (i.e. difference between LST at day and night) were the best predictors of schistosomiasis mansoni distribution in the study areas (Assaré et al., 2015). These risk factors were reported previously in other parts of the world and in Côte d'Ivoire (Raso et al., 2005; Schur et al., 2011; Chammartin et al., 2013; Walz et al., 2015).

With regard to environmental factors, we found that altitude was associated with *S. mansoni* infection, whilst living at an altitude of at least 400 m was associated with a lower risk of *S. mansoni* than living below. Similar results have been reported elsewhere in sub-Saharan Africa (Raso et al., 2005; Clements et al., 2006; Koroma et al., 2010). The altitude threshold limit for schistosomiasis transmission is a function of the study area. For instance, a previous study in Uganda revealed that there was no schistosomiasis case above 1,400 m above sea level (Kabaterine et al., 2004). In Heging county, People Republic of China, schistosomiasis-positive individuals can be found in locations as high as at 2,900 m (LI and LI, 2013). Therefore, there is a need to assess the altitude limit for schistosomiasis in the present study area by using several elevation strata in order to deepen our understanding of

schistosomiasis transmission. Our results showed that NDVI, land cover and soil type were not associated with *S. mansoni* infection (Assaré et al., 2015). In 2005, similar observations have been reported in the mountainous areas of Man in western Côte d'Ivoire (Raso et al., 2005; Beck-Worner et al., 2007). More recently, Chammartin and colleagues analysing national historical data of the country found only a moderate effect of soil type on the distribution of schistosomiasis mansoni (Chammartin et al., 2013). In contrast, previous studies in West and Eastern Africa found that these environmental covariates were strong predictors for schistosomiasis (Schur et al., 2011; Schur et al., 2013). One explanation might be the difference in scale of the Côte d'Ivoire studies (district level), compared to East and West Africa, studies (sub-continental level).

With regard to climatic factors, we found that the difference between LST at day and night was significantly associated with schistosomiasis (Assaré et al., 2015). The effect of temperature on schistosomiasis distribution is well documented (Hu et al., 2013; Scholte et al., 2014; Walz et al., 2015). Our results demonstrated that rainfall was not a good predictor for *S. mansoni* (Assaré et al., 2015). This observation confirms the result of previous studies in Tonkpi region (Beck-Worner et al., 2007). However, previous research revealed that rainfall is positively associated with schistosomiasis (Appleton, 1978; Jordan and Webbe, 1993; Sturrock, 1993). Underlying reasons for these differing observations might be issues in spatial scaling or setting-specific idiosyncrasies.

Regarding demographic factors, our study confirmed that sex and age are significantly associated with *S. mansoni* distribution (Assaré et al., 2015). It must be noted, however, that there are numerous other demographic covariates such socio-economic status, ethnicity, water contact behaviour and religion which might significantly influence the distribution of schistosomiasis. However, these were not included in the present investigation calling for future geospatial studies with a broader range of demographic covariates.

We observed very high *S. mansoni* prevalence ($\geq 50\%$) in the northern part of the Tonkpi region, while in the other parts of the study area the prevalence of the disease was mostly moderate to high (10–49%). Therefore, according to WHO guideline, school-aged children and other high-risk communities (such as fishermen) in northern Tonkpi region should be treated once a year with praziquantel, while in the remaining parts of the study areas, school-aged children should receive treatment once every two years.

On the micro-geographical scale, we found that rice cultivation, open defecation, use of traditional pit latrines, use of natural open fresh water bodies for washing and bathing were risk factors for schistosomiasis. These recreational and occupational activities have been

identified before as important risk factors influencing the transmission and spatial patterns of schistosomiasis (Sow et al., 2008; Schmidlin et al., 2013; Grimes et al., 2015). However, we did not assess the influence of these factors on *S. mansoni* transmission. In future studies, detailed parasitological, malacological and socio-economic factors should be investigated to deepen our understanding of risk factors of *S. mansoni* transmission forces in western Côte d'Ivoire.

6.3. Need for cost-effective MDA approach for sustainable control of schistosomiasis

Since the 1980s, WHO recommends preventive chemotherapy as the main pillar of the global schistosomiasis control strategy (WHO, 1985; 2002). However, the optimal timing period and frequency of MDA with praziquantel still needs to be determined for a more effective control of schistosomiasis in different settings (Colley, 2014).

This Ph.D. thesis contributes to strengthening the evidence-base of the cost-effectiveness of alternative MDA strategies that may be utilised to gain and sustain the control of schistosomiasis, and ultimately help to move to elimination. The developed study protocol describes a school-based cluster-randomised controlled trial that includes three treatment arms (A, B and C). Following the protocol design, schools of arm A are being treated once every year, schools of the treatment arm B receive MDA the first two years, followed by two years of “drug holidays”, while schools in treatment arm C receive MDA at baseline and at year three with “drug holidays” in the second and in fourth year (Assaré et al., 2014). Treatment arm A, where school-aged children receive annual MDA (subjected to the highest drug pressure), represents the benchmark intervention. It is well known that repeated praziquantel dosing leads to marked reductions in the prevalence and intensity of infection (Magnussen et al., 1997; King et al., 2011; Sesay et al., 2014). However, repeated MDA and community fatigue are major challenges to obtain high and sustained treatment coverage rates, which might increase treatment costs to an unexpected high level for governments of endemic countries where financial resources are generally limited (Brooker et al., 2008; Leslie et al., 2011). For example, although in sub-Saharan Africa governments often receive praziquantel free of charge, they do not have sufficient financial resources to distribute several millions of tablets annually across to remote “hard to reach” areas where health centers and schools are often rare (Hodges et al., 2012). Thus, additional financial resources are required for covering the cost related to equipment, transport, information education communication materials,

training materials, and “per diems” (Fenwick, 2015). In our SCORE study, it is conceivable that treatment arm A is the intervention arm that will produce the largest reduction of schistosomiasis among children and showed to be the most effective in terms of morbidity reduction; however, this treatment arm is also the most expensive one. Therefore, it is relevant to determine a control strategy that provides the best balance in terms of costs and reductions of morbidity due to schistosomiasis. Treatments arms B and C include “drug holidays” hence these arms are considerably less expensive but exert a lower drug pressure. Long periods of “drug holiday” might be associated with re-infection among cured individuals. Both treatment arms include two years of drug holidays. However, in treatment arm B the two years of drug holiday (years 3 and 4) are consecutive, while in treatment arm C, the two years of drug holidays (year 2 and 4) are interspaced by a year of MDA (year 3). Therefore, the population in treatment arm B is more likely to be subjected to re-infection compared to the populations in treatment arms A and C. At the end of the study, we should be able to have a definitive answer on whether the treatment strategy with more (treatment arm B) or less (treatment arm C) extensive subjection to schistosomiasis re-infection is the better strategy in reducing schistosomiasis prevalence and intensity in moderate endemicity settings.

6.4. Impact of MDA on schistosomiasis mansoni

Praziquantel is the human schistosomiasis drug of choice as recommended by WHO (WHO, 2002). Several studies have reported that MDA with praziquantel termed preventive chemotherapy could reduce the schistosomiasis prevalence and intensity, control morbidity and limit the transmission within endemic areas (Utzing et al., 2000a; WHO, 2002; Raso et al., 2004b; Bockarie et al., 2013). In early 2012, numerous pharmaceutical companies and international donors endorsed the London declaration on neglected tropical diseases (WHO, 2012). In line with this declaration, the company Merck KGaA promised to distribute 250 million tablets of praziquantel in schistosomiasis endemic countries until the elimination of the disease (WHO, 2012). In 2013, more than 26 million people in Africa received praziquantel treatment (WHO, 2015). WHO recommended achieving at least coverage of 75% in endemic area by 2020. However, the intensive MDA with praziquantel lead to numerous concerns including failure to reduce schistosomiasis prevalence and intensity, low coverage and compliance and potential drug resistance (Wang et al., 2012; Ross et al., 2015; Tuhebwe et al., 2015). The current study assesses the impact of MDA with praziquantel on schistosomiasis mansoni in western Côte d’Ivoire one year post-treatment (Assaré et al.,

2016b). We found that an overall coverage of 84.2% was achieved. The overall *S. mansoni* prevalence decreased, while the intensity of the infection increased.

The overall coverage in the study area reached the WHO target and 75% coverage was achieved in the majority of the schools (76%). The higher coverage can be explained by the combined school- and community-based MDA strategies targeting school-age children. Indeed, in addition to the schools, the treatment was implemented in the communities in order to reach the maximum of school-age children. Another explanation might be the information, education and communication (IEC) strategy implemented. First, at the start of the study and before the parasitological survey, a team was designated to talk to district and village authorities, teachers and children's parents and offer detailed information about schistosomiasis, the objectives and procedures of the study (Assaré et al., 2014). Second, before the implementation of the MDA, different IEC tools such as radio and television announcements were used to sensitize the communities (Assaré et al., 2014). These diverse IEC approaches may have resulted in better MDA compliance, and thus higher coverage (Schall, 1995; Utzinger et al., 2005; Omedo et al., 2014b). In addition, the praziquantel delivery to schoolchildren and non-school attendees was carried out by school teachers. Before the MDA, school teachers were well trained in drug administration (Assaré et al., 2014). The contribution of school teachers in helminth control programs and particularly the in MDA success was described elsewhere (Belizario et al., 2013).

Although a high overall coverage was reported, low coverage was observed in few schools (24%), specifically in Yaoudé where a coverage rate of 31.9% was achieved. The low coverage in some schools might be due to many factors including lack of knowledge on schistosomiasis prevention, religious objection, misconception from the community members, conspiracy theories about the "real" purpose of treatment, and in particular the experiences of side effects (Raso et al., 2004b; Omedo et al., 2014a; Muhumuza et al., 2015). In Côte d'Ivoire, previous praziquantel-based interventions induced several mild and transient side effects such as abdominal pain, dizziness and (bloody) diarrhea (N'Goran et al., 2003; Raso et al., 2004b). However, subjects harboring a high intensity of schistosomiasis can suffer from severe side effects (Utzinger and Keiser, 2004). In villages with low treatment coverage, sensitization and health education needs to be strengthened in order to resolve the fear of the treatment side effects and increase the MDA compliance.

Our findings showed that one year post-MDA the overall *S. mansoni* prevalence dropped, while the intensity of the infection increased (Assaré et al., 2016b). This finding may suggest behaviour changes among school-age children due to IEC approaches. Another

plausible reason for the variation in infection intensity could be a lack of reliability of the Kato Katz technique to accurately determine worm burdens (Kongs et al., 2001; Utzinger et al., 2001; Sayasone et al., 2015). This result may also reflect that the transmission was uninterrupted after the praziquantel treatment. Indeed, the preventive chemotherapy does not prevent re-infection nor does it stop the life cycle of the parasite (Gray et al., 2010; Garba et al., 2013). First, we found that rice cultivation, washing and bathing in open fresh water were practiced and were common in the villages surveyed. These occupational and recreational activities may expose the populations of the study area to get in contact with contaminated water. Therefore, they are permanently exposed to schistosomiasis re-infection. Second, during the MDA adult, pregnant women, sick school-age children and particularly young children (children aged below five years of age) were not treated. Thus, these categories of people may ensure the continuity of the infection transmission. On one hand, this finding calls for the need to adopt an integrated approach to sustainable control schistosomiasis as underscored by other studies (Utzinger et al., 2003; Utzinger et al., 2009). On the other hand, this result may reveal the relevance to determine the best frequency of the MDA to decrease schistosomiasis prevalence to low level endemicity (Assaré et al., 2014; Colley, 2014). There are notable shortcomings of the study; first, the intensity of the infection was expressed based on the AM EPG among only the infected individuals (Montresor et al., 1998). Second, the present randomised controlled trial is an opened research. It is possible that a part of the infected individuals did not receive treatment at baseline because of specific reason. Some school-age children were, for instance, not treated because they were sick, absent or lived outside the study area. These untreated positive individuals might have increase the intensity of the infection.

Our data revealed that the proportion of children harboring heavy *S. mansoni* infection intensity was higher among first graders compared with 9–12 years old children. Based on this trend we state that there were some young children who might harbor heavy infection intensity. Heavy *S. mansoni* infection among young children was reported in Côte d'Ivoire and Sierra Leone (Hodges et al., 2012; Coulibaly et al., 2013a; Coulibaly et al., 2013b). These observations confirm the need to consider the treatment of young children in sub-Saharan Africa in order to successfully control schistosomiasis (Ekpo et al., 2012; Coulibaly et al., 2013b; Stothard et al., 2013).

6.5. Conclusion

The starting point of this Ph.D. thesis was to deepen our understanding of the epidemiology of schistosomiasis mansoni and to determine an appropriate strategy to sustainably control the disease.

First, we developed a 5-year school-based research protocol which will allow us to determine a cost-effective MDA strategy for sustaining schistosomiasis control. Second, a rapid parasitological assessment was conducted in four regions of western Côte d'Ivoire to select 75 schools with moderate schistosomiasis endemicity. Based on the available data, risk and prediction maps for schistosomiasis mansoni were generated. Third, rigorous parasitological surveys were carried out in the selected schools to determine the baseline situation of the local communities. Concomitantly, a questionnaire was delivered to collect social-ecological data which might influence the occurrence of the disease. After baseline parasitological surveys the initial school- and community-based MDA with praziquantel targeting school-age children was carried out in all villages of the study area. Finally, one year post-MDA a parasitological assessment was conducted to evaluate the effect of the initial MDA on schistosomiasis mansoni. Based on the result of the work presented in this thesis, the following conclusions can be drawn:

- * A 4-year cluster randomized control study protocol was designed and the trial is taking place. At the end of this study the most cost-effective MDA will be determined and should allow to better control schistosomiasis morbidity at a lower cost. Therefore, it will contribute to reduce the poverty.
- * Age, sex, altitude and difference between land surface temperature at day and night were correlated with *S. mansoni* infection at macro-geographical level, while rice cultivation, washing, bathing in fresh water bodies and open defecation were the potential factors associated with the disease at micro-geographical level. The risk and predicted maps generated are useful for future schistosomiasis control programmes.
- * At baseline survey parasitological and socio-ecological characteristics of local communities were determined and will be relevant for the ongoing randomized controlled trial. Moreover, we found that the increase of the sampling effort leads to an increase in the sensitivity of the Kato-Katz technique. In addition, the fragility of the classification of communities based on WHO criteria was highlighted.
- * One year post-MDA, the overall prevalence of *S. mansoni* decreased while the intensity of the infection increased. The transmission dynamics were heterogeneous

varying from one village to another. This observation calls for an integrated approach to successfully control schistosomiasis.

6.6. Recommendations

- * Malacological and parasitological should be implemented to deepen our understanding in the schistosomiasis mansoni dynamics across the communities.
- * Parasitological survey coupled with questionnaire including socio-economic, demographic and environmental factors should be administered at household level to confirm the association of these factors with *S. mansoni* at community level.
- * Intensification of the IEC approach in the community with treatment coverage lower than 75%.
- * To improve the involvement and the motivation of the community health workers in order to increase the treatment coverage.
- * Annual assessment of the impact of the MDA on schistosomiasis to better evaluate the changes of schistosomiasis mansoni over time.
- * Young children should be considered during the MDA. This can increase the effect of the MDA on the disease transmission.
- * Integrated approach including MDA, IEC and snail control to successfully control schistosomiasis in the four region of western Côte d'Ivoire.

6.7. References

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7. Curriculum vitae

Curriculum vitae

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Qualification

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 University)
 23-24/02/2015 Course of Swiss School of Public Health Plus;
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 Supervision: Dr. Jan Hattendorf
 10-13/10/2014 Course of Swiss School of Public Health Plus; "GIS for
 Public Health" (Basel, Switzerland)

Supervision: Dr. Danielle Vienneau

01/08/2013-10/09/2013 Summer student at International Graduate School North-South, Centre Suisse de Recherches Scientifiques en Côte d'Ivoire on "Health and Environment" (Abidjan (Grand-Bassam), Côte d'Ivoire)

Supervision: Dr. Karl Herweg

2010

M. Sc (Diploma) in Entomology

Université Félix Houphouët-Boigny, Côte d'Ivoire

Thesis title: Préférences trophiques de *Anopheles gambiae s. l.* en milieu urbain: cas d'Adzopé, Côte d'Ivoire

Supervision: Prof. Dr. Eliézer Kouakou N'Goran (Université Félix Houphouët-Boigny)

2004

BSc Bachelor of Sciences in Biology, Major in Animal Science (Université de Cocody, Côte d'Ivoire)

Oral presentation and scientific meetings

09/03/2016 Talk at the Congrès de la Société Ivoirienne de Parasitologie et de Mycologie: Lutte durable contre la schistosomiase à *Schistosoma mansoni* dans l'ouest de la Côte d'Ivoire, résultats d'une étude de SCORE un an après le traitement initial au praziquantel.

04/05/2015 Talk at the annual Ph.D.-student meeting (2015) at Swiss Tropical and Public health Institute: "Sustaining control of schistosomiasis mansoni in moderate endemicity areas in western Côte d'Ivoire: a SCORE study protocol" (Basel, Switzerland)

16-19/07/2014 Talk at the PARATROP 2014 (Join Society Meeting of Parasitology and Tropical Medicine) at the University of Zurich: "Control of *Schistosoma mansoni* in western Côte d'Ivoire: baseline

findings before the implementation of a randomized trial” (Zurich, Switzerland)

8. Publications

Assaré, R. K., Knopp, S., N'Guessan, N. A., Yapi, A., Tian-Bi, Y.-N.T., Yao, P.K., Coulibaly, J. T., Ouattara, M., Meïté, A., Fenwick, A., N'Goran, E. K., Utzinger, J. (2014) Sustaining control of schistosomiasis mansoni in moderate endemicity areas in western Côte d'Ivoire: a SCORE study protocol. *BMC Public Health* (14): 1290.

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Lai, Y.-S., Biedermann, P., Ekpo, U. F., Garba, A., Mathieu, E., Midzi, N., Mwinzi, P., N'Goran, E. K., Raso, G., **Assaré, R. K.**, Sacko, M., Schur, N., Talla, I., Tchuem Tchuenté, L. –A., Touré, S., Winkler, M. S., Utzinger, J., Vounatsou, P. (2015) Spatial distribution of schistosomiasis and treatment needs in sub-Saharan Africa: a systematic review and geostatistical analysis. *Lancet Infect Dis* (15): 927-940.

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