Enhancing control of schistosomiasis in Niger: assessing morbidity in preschool-aged children, praziquantel treatment efficacy and cost implication for control

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List of abbreviations

AIDS	Acquired immunodeficiency syndrome
BMGF	Bill & Melinda Gates Foundation
CCA	Circulating cathodic antigen
CDD	Community drug distributor
CERMES	Centre de Recherche Médicale et Sanitaire
CFA	Communauté financière africaine (West Africa francophone countries currency)
CI	Confidence interval
CNRST	National Centre for Scientific and Technical Research (Centre National de la Recherche Scientifique et Technique; Burkina Faso)
CNTD	Centre for Neglected Tropical Diseases
ComDT	Community directed treatment
CONTRAST	A multidisciplinary alliance to optimize schistosomiasis control and transmission surveillance in sub-Saharan Africa (an EU-funded research project)
CR	Cure rate
CWW	Children Without Worms
DALY	Disability-adjusted life year
DBL	Danish Bilharziasis Laboratory
DFID	Department for International Development
ECP	Eosinophil cationic protein
EPG	Egg per gram of stool
ERR	Egg reduction rate
EU	European Union
GIS	Geographical information system
GM	Geometric mean
HIV	Human immunodeficiency virus
ICL	Imperial College London
IEC	Information, education and communication
INRSP	National Institute for Research in Public Health/ Institut National de la Recherche en Santé Publique (Mali)
IRD	French Institute for Research for Development (Institut de Recherche pour le Developpement)
IRSS	Centre of Research in Health Sciences (Centre de Recherche en Sciences de la Santé; Burkina Faso)

IT	Information technology
LQAS	Lot quality assurance sampling
MDA	Mass drug administration
MoH	Ministry of Health
NER	Net enrolment rate
NGO	Non-governmental organization
NHM	Natural History Museum
NRV	Niger River Valley
NTD	Neglected tropical disease
PCR	Polymerase chain reaction
PCT	Preventive chemotherapy
PNLBG	Niger National Programme for Control of Schistosomiasis and Soil-Transmitted Helminths (Programme National de Lutte contre la Bilharziose et les Geohelminthes)
PZQ	Praziquantel
RISEAL	Réseau International Schistosomose, Environnement, Aménagement et Lutte (an NGO that aims at reinforcing research and control of schistosomiasis in Africa)
RTI	Research Triangle International
SCI	Schistosomiasis Control Initiative
SCORE	Schistosomiasis Consortium for Operational Research and Evaluation
SD	Standard deviation
SEA-ELISA	Soluble egg antigen-enzyme-linked immunosorbent assay
Sh	*Schistosoma haematobium*
Sm	*Schistosoma mansoni*
SSA	Sub-Saharan Africa
STH	Soil-transmitted helminthiasis
Swiss TPH	Swiss Tropical and Public Health Institute
UK	United Kingdom
USAID	United States Agency for International Development
WHA	World Health Assembly
WHO	World Health Organization

Summary

Background: Schistosomiasis, accounted among the neglected tropical diseases (NTDs), represents a major public health problem, particularly in Africa, where more than 95% of all the cases of the world are currently concentrated. The health consequences of *Schistosoma* infection are considerable. Apart from the known long-term complications of a chronic infection (e.g. portal hypertension, kidney failure, bladder cancer and sterility), schistosomiasis is a debilitating disease leading to anaemia, malnutrition, chronic abdominal and pelvic pain, and diarrhoea.

In 2001, the World Health Assembly (WHA) adopted resolution 54.19, which urged member states to regularly treat at least 75% and up to 100% of all school-aged children at risk of schistosomiasis and other high-risk groups. Moreover, in 2006, the World Health Organization (WHO) launched the "preventive chemotherapy" (PCT) strategy, which relies on the regular administration of anthelminthic drugs to at-risk populations in an integrated manner. Following these international calls for action against NTDs, several African countries, including Niger, launched national control programmes based on PCT with support from partners.

The aims of the present PhD thesis in epidemiology were (i) to assess the morbidity of schistosomiasis in infants and preschool-aged children currently not included in PCT; (ii) to evaluate praziquantel (PZQ) efficacy using different treatment schemes, including a detailed analysis of cost; and (iii) to enhance the control of schistosomiasis and other NTDs in Niger.

Methods and principal findings: First, achievements and remaining challenges of schistosomiasis and soil-transmitted helminthiasis (STH) control in three countries of West Africa (i.e. Burkina Faso, Mali and Niger) that benefited from support of the Schistosomiasis Control Initiative (SCI) have been analysed. In the first 3 years of the control programmes, nearly 13.5 million doses of PZQ have been administrated against schistosomiasis and albendazole against STH with coverage rates varying between 67% and 94%. The PZQ treatments have resulted in a reduction of the prevalence and intensity of *Schistosoma* infection in sentinel cohorts that were set up to monitor and evaluate the national control programmes. Key challenges these national control programmes are currently facing include the ability to maintain the reduction in morbidity achieved so far and ensuring sustainability.

Second, we assessed morbidity due to schistosomiasis in infants and preschool-aged children who are currently not included in PCT according to WHO guidelines, including risk factors for infection in early childhood. We carried out a cross-sectional epidemiological survey in two villages in Niger: Falmado that is endemic for *Schistosoma haematobium* only, and Diambala that is a mixed *S. haematobium-S. mansoni* focus. A total of 282 children were examined (149 girls, 133 boys; average age, 2.6 years) and 224 mothers (average age, 30.1 years). For *S. haematobium* diagnosis, two urine samples obtained over consecutive days were subjected to a standard filtration method, while the diagnosis of *S. mansoni* was based on a single stool sample using duplicate Kato-Katz thick smears. Additionally, in Diambala, a pre-tested questionnaire was administered to mothers, which recorded demographic data, recent treatment history with anthelminthic drugs, household sanitation and water supply and bathing practices for their children. Prevalence of egg-patent *S. haematobium* infection among young children and their mothers was, respectively, 51% and 56% in Falmado, and 61% and 72% in Diambala. The prevalence of *S. mansoni* infection in Diambala was 44% among children and 52% in mothers. Mixed egg-patent infections of *S. haematobium* and *S. mansoni* were revealed in 29% of the children and 37% of the mothers. Results from the questionnaire survey showed that 70% of the children were accompanied by their mothers to schistosomiasis transmission sites before reaching their first birthday, and that three-quarter of the mothers used water directly drawn from the irrigation canals to wash their children.

Third, we evaluated the efficacy and safety of two closely spaced doses of PZQ against *S. haematobium* and *S. mansoni* in school-aged children, and characterised re-infection patterns over a 1-year period. The study was carried out in five villages in western Niger: Falmado, Seberi, Diambala, Namarigoungou and Libore. Parasitological examinations consisted of triplicate urine filtrations and triplicate Kato-Katz thick smears at each visit. Two 40 mg/kg oral doses of PZQ were administered 3 weeks apart. Follow-up visits were conducted 6 weeks, 6 months and 12 months after the first dose of PZQ. Adverse events were monitored within 4 hours after dosing by the survey team and 24 hours after treatment using a questionnaire. Our final study cohort comprised 877 children who were infected with either *S. haematobium*, or *S. mansoni*, or both species concurrently and received both doses of PZQ. At baseline, the geometric mean (GM) infection intensity of *S. haematobium* ranged from 3.6 (Diambala) to 30.3 eggs/10 ml of urine (Falmado). The GM infection intensity of *S. mansoni* ranged from 86.7 (Diambala) to 151.4 eggs/gram of stool (EPG) (Namarigoungou). Adverse events were reported by 33% and 1.5% of the children after the first and second dose of PZQ,

respectively. We found cure rates in *S. haematobium*-infected children 3 weeks after the second dose of PZQ ranging between 49% (Falmado) and 98% (Namarigoungou) and high egg reduction rates (92-100%). Regarding *S. mansoni*, only moderate cure and egg reduction rates were found (52-59% in Diambala, 55-60% in Namarigoungou).

Fourth, in order to generate additional evidence regarding the safety and efficacy of PZQ for schistosomiasis in infants and preschool-aged children, we pursued a drug efficacy trial using PZQ syrup (Epiquantel®) in children aged below 72 months. The study was carried out between May and August 2010 in three villages. Overall, 243 children infected with *S. haematobium* and/or *S. mansoni* were treated with PZQ syrup at a dose of 40 mg/kg after they had received a meal of millet porridge. Children were observed during 4 hours post-treatment and a questionnaire was administered to the mothers the following day to determine adverse events. Follow-up visits consisting of three urine filtrations and triplicate Kato-Katz thick smears were conducted 3 and 6 weeks post-treatment. The proportion of children having presented early adverse events during the 4-hour period post-treatment was 33% and the proportion of adverse events occurring within 24 hours after treatment was 6.2%. No serious adverse events were recorded. The most frequent symptoms were abdominal pains (31%), bloody diarrhoea (16.2%) and sleepiness (15.3%). Before treatment, 165 children were infected with *S. haematobium* among whom 87% presented a light infection (1-49 eggs/10 ml of urine) and 13% a heavy infection (≥50 eggs/10 ml of urine). The overall cure rate against *S. haematobium* was 86% and 95% after 3 and 6 weeks post-treatment, respectively. Three and 6 months after treatment, the GM egg reduction rate for *S. haematobium* was 69% and 71%, respectively. With regard to *S. mansoni*, 96 infected children, were treated with PZQ. Among them, 39% had moderated to heavy infection intensities (≥100 EPG). Observed cure rates were 75% and 50%, respectively, 3 and 6 weeks after treatment. The respective GM egg reduction rates were 67% and 19%.

Fifth, in order to help countries in finding viable strategies that are financially acceptable to sustain schistosomiasis control activities, we conducted a cost-effectiveness study comparing a school-based and a community-based mass drug administration strategy for schistosomiasis and STH control in Niger. In 2006, we undertook a survey in four districts to estimate the economic cost per district, per treatment and per *Schistosoma* infection averted. The study compared the costs of treatment at start-up and in a subsequent year and identified the allocation of costs by activity, input and organization. The total economic cost of the

programme, including programme-specific expenditures, national and local government costs and international technical support and programme co-ordination in four study districts, over a 2-year period, was US$ 456,718, which translates to an economic cost per treatment of US$ 0.58. The full economic delivery cost of school-based treatment in 2005/2006 was US$ 0.76, while a somewhat lower cost was observed for community distribution (US$ 0.46). If only costs to the programme were included, the respective figures were US$ 0.47 and US$ 0.41. In the study district over a 2-year period, the average cost per *Schistosoma* infection averted was US$ 0.76 for children with one treatment and the cost was US$ 6.7 for adults.

Conclusions: Sustainability of schistosomiasis and STH control programmes in sub-Saharan Africa remains a grand challenge. Integration with other existing health interventions, particularly those targeting NTDs and strengthening of health systems is a way to ensure continued distribution of anthelminthic drugs and other interventions. At an average cost per treatment of US$ 0.58, control could be handled by the countries.

A substantive proportion of preschool-aged children had egg-patent *Schistosoma* infection, inclusive of co-infection with *S. haematobium* and *S. mansoni*. Hence, in highly endemic areas, more attention should be paid on preschool-aged children and women of childbearing age, so that they can benefit from PCT, thus, increasing effective coverage of those infected. PZQ syrup is well tolerated in infants and preschool-aged children. The cure and eggs reduction rates were high against *S. haematobium* infection, but additional studies are warranted to determine the efficacy against *S. mansoni*.

In school-aged children, PZQ given in two closely spaced doses is efficacious against *S. haematobium*. However, low egg reduction rate observed against *S. mansoni* raises concern about mounting PZQ tolerance.

Zusammenfassung

Hintergrund: Schistosomiasis ist eine vernachlässigte tropische Krankheit, welche ein bedeutendes Problem für die öffentliche Gesundheit darstellt, vor allem in Afrika, wo aktuell mehr als 95% aller weltweit auftretenden Fälle konzentriert sind. Die gesundheitlichen Auswirkungen der Schistosomiasis sind beträchtlich. Abgesehen von den bekannten Langzeit Komplikationen einer chronischen Infektion (wie Pfortaderhochdruck, Leberversagen, Blasenkrebs und Unfruchtbarkeit) ist Schistosomiasis eine kräftezehrende Erkrankung welche zu Anämie, Mangelernährung, chronischen Unterleibsschmerzen sowie Diarrhö führen kann.

Im Mai 2001 wurde an der ‘‘World Health Assembly“ (WHA) die Resolution Nummer 54.19 ins Leben gerufen. Diese Resolution hält Mitgliederstaaten dazu an regelmässig mindestens 75% und bis 100% aller Kinder im Schulalter, welche dem Risiko einer Schistosomen Infektion ausgesetzt sind, sowie andere Gruppen mit hohem Risiko, regelmässig mit Praziquantel zu behandeln. Desweiteren führte die Weltgesundheitsorganisation (WHO) eine Strategie der „präventiven Chemotherapie“ (PCT) ein, welche sich auf eine regelmässige, integrative Verabreichung von Entwurmungsmitteln stützt. Diesen internationalen Aufrufen für die Bekämpfung der Schistosomiasis und anderer vernachlässigter Tropenkrankheiten folgend, lancierten einige afrikanische Länder, einschliesslich Niger, mit Hilfe von Partnern, PCT-basierte, nationale Kontrollprogramme.

Die Ziele dieser Dissertation in Epidemiologie waren (i) die Morbidität durch Schistosomiasis in Klein- und Vorschulkindern, welche derzeit nicht in die PCT Strategie eingeschlossen sind, zu ermessen; (ii) die Wirksamkeit und Verträglichkeit von Praziquantel bei verschiedenen Behandlungsschemata zu evaluieren, einschliesslich einer detaillierten Kostenanalyse; und (iii) die Kontrolle der Schistosomiasis und anderer vernachlässigter Tropenkrankheiten in Niger zu stärken.

Methoden und wichtigste Ergebnisse: Zuerst wurden die bisherigen Leistungen und verbleibenden Herausforderungen der Schistosomiasis und der vom Boden-übertragenen Wurminfektionen in drei Ländern Westafrikas (nämlich Burkina Faso, Mali und Niger), welche von der Unterstützung der “Schistosomiasis Control Initiative“ (SCI) profitierten, analysiert. In den ersten drei Jahren des Kontrollprogramms wurden annähernd 13.5 Millionen Dosen Praziquantel gegen Schistosomiasis, und Alendazole gegen von Boden-übertragenen Wurminfektionen verabreicht mit einer Deckungsrate zwischen 67% und 94%.

Die Praziquantel Behandlungen führten zu einer Reduktion der Prävalenz und Intensität von Schistosomen Infektionen in den Beobachtungskohorten welche zur Überwachung und Bewertung der nationalen Kontrollprogramme etabliert worden waren. Die Schlüsselherausvorderungen welchen diese nationalen Kontrollprogramme derzeit gegenüber stehen, sind das Vermögen, diesen Rückgang der Morbidität welcher bisher erreicht wurde beizubehalten sowie die Sicherung der Nachhaltigkeit.

Zweitens ermassen wir die Morbidität von Schistosomiasis in Klein- und Vorschulkindern, welche zur Zeit nicht in der PCT wie von der WHO empfohlen eingeschlossen sind, einschliesslich der Risikofaktoren einer Infektion in der frühen Kindheit. Wir führten eine Querschnittsstudie in zwei Dörfern in Niger durch: Falmado welches endemisch nur für *Schistosoma haematobium* ist und Diambala welches ein Brennpunkt sowohl für *S. haematobium* wie auch *S. mansoni* ist. Insgesamt wurden 282 Kinder (149 Mädchen, 133 Jungen; durchschnittliches Alter: 2.6 Jahre) und 224 Mütter (durchschnittliches Alter: 30.1 Jahre) untersucht. Für die Diagnose von *S. haematobium* wurden zwei Urinproben an zwei aufeinanderfolgenden Tagen mit der Standard Filtrationsmethode untersucht, während die Diagnose von *S. mansoni* auf der Untersuchung einer einzelnen Stuhlprobe mittels zweier Kato-Katz Ausstriche beruhte. Desweiteren wurden vorgetestete Fragebögen, welche demographische Daten, kürzliche Behandlungsgeschichten mit Entwurmungsmitteln, die sanitäre Situation des Haushalts und Wasserversorgung sowie Badepraktiken für die Kinder aufnahmen, mit den Müttern in Diambala durchgeführt. Die Prävalenz von Ei-patenten *S. haematobium* Infektionen bei jungen Kindern und deren Mütter war 51% und 56% in Falmado, sowie 61% und 72% und Diambala. Die Prävalenz von *S. mansoni* in Diambala war 44% unter den Kindern und 72% unter den Müttern. Gemischte, Ei-patente Infektionen von *S. haematobium* und *S. mansoni* zeigten sich in 29% der Kinder und 37% der Mütter. Die Auswertung der Fragebogenstudie zeigte, dass 70% aller Kinder von ihren Müttern zu Schistosomiasis Übertragungsstellen begleitet wurden, bevor sie ein Jahr alt waren und dass drei-Viertel der Mütter Wasser welches sie direkt aus den Bewässerungskanälen bezogen benutzten um ihre Kinder zu waschen.

Drittens evaluierten wir die Wirksamkeit und Sicherheit zweier eng aufeinanderfolgender Dosen Praziquantel gegen *S. haematobium* und *S. mansoni* bei Kindern im Schulalter und charaktisierten die Re-infektionsmuster über einen Zeitraum von einem Jahr. Die Studie wurde in den folgenden fünf Dörfern im Westen Nigers durchgeführt: Falmado, Seberi,

Diambala, Namarigoungou und Libore. Parasitologische Untersuchungen bestanden aus drei Urinfiltrationen und drei Kato-Katz Ausstrichen bei jedem Besuch. Zwei 40 mg/kg Praziquantel Dosen wurden in einem Abstand von drei Wochen verabreicht. Folgebesuche wurden 6 Wochen, 6 Monate und 12 Monate nach der ersten Praziquantel Dosis durchgeführt. Nebenwirkungen wurden während vier Stunden nach der Medikamentenverabreichung vom Studienteam, und 24 Stunden danach mittels eines Fragebogens überwacht. Unsere letztendliche Studienkohorte bestand aus 877 Kindern die entweder mit *S. haematobium* oder *S. mansoni* oder mit beiden parasitären Wurmarten zugleich infiziert waren und beide Dosen Praziquantel erhalten hatten. Bei der Basisstudie reichte der geometrische Mittelwert (GM) der Infektionsintensität von *S. haematobium* von 3.6 (Diambala) bis 30.3 Eier pro 10 ml Urin (Falmado). Der GM der Infektionsintensität von *S. mansoni* reichte von 86.7 (Diambala) bis 151.4 Eier pro Gramm Stuhl (EPG) (Namarigoungou). Nebenwirkungen wurden bei 33% bzw. 1.5% der Kinder nach der ersten bzw. zweiten Dosis Praziquantel berichtet. Wir fanden Heilungsraten zwischen 49% (Falmado) und 98% (Namarigoungou) sowie hohe Ei Reduktionsraten (92-100%) bei *S. haematobium*-infizierten Kindern drei Wochen nach Verabreichung der zweiten Praziquantel Dosis. Für *S. mansoni* wurden lediglich mittelmässige Heilungs- und Ei Reduktionsraten gefunden (52-59% in Diambala, 55-60% in Namarigoungou).

Viertens führten wir, um weitere Befunde bezüglich der Verträglichkeit und Wirksamkeit von Praziquantel gegen Schistosomiasis bei Klein- und Vorschulkindern zu erhalten, eine Wirksamkeitsstudie mit einem Praziquantel Sirup (Epiquantel®) bei Kindern mit einem Alter von bis zu 72 Monaten durch. Die Studie wurde zwischen Mai und August 2010 in drei Dörfern in Niger durchgeführt. Insgesamt wurden 243 Kinder welche mit *S. haematobium* und/oder *S. mansoni* infiziert waren, mit einer Dosis von 40 mg/kg des Praziquantel Sirups behandelt, nachdem ihnen eine Mahlzeit aus Hirsebrei verabreicht worden war. Nach der Behandlung wurden die Kinder über 4 Stunden beobachtet und am darauffolgenden Tag ein Fragebogen mit den Müttern durchgeführt um Nebenwirkungen zu ermitteln. Folgeuntersuchungen bestehend aus 3 Urinfiltrationen und 3 Kato-Katz Ausstrichen wurden 3 und 6 Wochen nach der Behandlung durchgeführt. Der Anteil Kinder, der frühe Nebenwirkungen während der ersten 4 Stunden nach Behandlung zeigte, lag bei 33% und der Anteil Nebenwirkungen welche innerhalb von 4-24 Stunden nach der Behandlung auftraten bei 6.1%. Es wurden keine ernsten Nebenwirkungen berichtet. Die am häufigsten auftretenden Symptome waren Unterleibsschmerzen (31%) sowie blutiger Durchfall und

Schläfrigkeit (16%). Vor der Behandlung waren 166 Kinder mit *S. haematobium* infiziert, von welchen 87% eine leichte Infektion (1-49 Eier pro 10 ml Urin) und 13% eine schwere Infektion (≥50 Eier pro 10 ml Urin) aufwiesen. Die Heilungsrate für *S. haematobium* betrug im Gesamten 86% drei Wochen, bzw. 95% sechs Wochen nach Behandlung. Der GM der Ei Reduktionsrate für *S. haematobium* betrug 71% drei, bzw. 77% sechs Wochen nach Behandlung. Gegen *S. mansoni* wurden 96 infizierte Kinder mit Praziquantel behandelt. Unter diesen hatten 39% eine mittlere bis schwere Infektion (≥100 EPG). Die beobachtete Heilungsrate lag bei 75% drei, bzw. 50% sechs Wochen nach Behandlung. Die entsprechenden GM der Ei Reduktionsraten waren 67% und 19%.

Fünftens, um den Ländern dabei zu helfen durchführbare Strategien dafür zu finden die Schistosomiasis Kontrollstrategien langfristig zu gewährleisten, führten wir eine Kosteneffizienzstudie durch in welcher wir eine schulbasierte mit einer gemeindebasierten Massenbehandlungsstrategie gegen die Schistosomiasis und von Boden-übertragener Wurminfektionen verglichen. Unsere Studie wurde im Jahr 2006 durchgeführt in vier Distrikten von Niger um die wirtschaftlichen Kosten pro Distrikt, pro Behandlung und pro abgewendeter Schistosomen Infektion abzuschätzen. In der Studie wurden die Behandlungskosten beim Start und im darauffolgenden Jahr verglichen und die Kostenverteilung auf die Aktivitäten, den Einsatz und die Organisation identifiziert. Die gesamten wirtschaftlichen Kosten des Programms, einschliesslich programmspezifischer Ausgaben, nationaler und lokaler Regierungskosten und internationaler technischer Unterstützung sowie Programmkoordination von vier Distrikten betrugen 456,718 US$ über einen Zeitraum von zwei Jahren, was einem Kostenpunkt von 0.58 US$ pro Behandlung entspricht. Die vollen wirtschaftlichen Kosten für eine schulbasierte Behandlung in Jahr 2005/2006 betrugen 0.76 US$ während für die gemeindebasierte Behandlung etwas niedrigere Kosten beobachtet wurden (0.46 US$). Wenn man für die jeweiligen Grafiken ausschliesslich die Kosten des Programms berücksichtigt, handelt es sich um 0.47 US$ bzw. 0.41US$. Die durchschnittlichen Kosten pro abgewandter Schistosomen Infektion im Studiengebiet über den Zeitraum von zwei Jahren betrugen 0.76 US$ für Kinder mit einer Behandlung und 6.7 US$ für Erwachsene.

Schlussfolgerungen: Die Nachhaltigkeit von Kontrollprogrammen gegen die Schistosomiasis und anderer vernachlässigter Tropenkrankeiten in Subsahara-Afrika bleibt eine gewaltige Herausforderung. Die Eingliederung in andere Gesundheitsinterventionen, vor

allem jener welche auf vernachlässigte Tropenkrankheiten und die Stärkung von Gesundheitssystemen abzielen, stellt einen Weg dar, um die kontinuierliche Verteilung von Entwurmungsmedikamenten und anderer Interventionen sicher zu stellen. Wir spekulieren, dass die durchschnittlichen Kosten von 0.58 US$ pro Behandlung von den Ländern gehandhabt werden können.

Ein bedeutender Anteil Vorschulkinder hatte eine Ei-patente Schistosomen Infektion, inklusive Co-Infektion zwischen *S. haematobium* und *S. mansoni*. Daher sollte in hochendemischen Gebieten Vorschulkindern und Frauen im gebährfähigen Alter mehr Aufmerksamkeit geschenkt werden, damit sie von der PCT profitieren und so die effektive Abdeckung der Infizierten erhöht wird. Praziquantel Sirup wird von Klein- und Vorschulkindern gut vertragen. Gute Heilungsraten und hohe Ei Reduktionsraten wurden bei der *S. haematobium* gefunden, doch weitere Studien sind angebracht um die Wirksamkeit gegen *S. mansoni* zu bestimmen.

Bei Kindern im Schulalter ist Praziquantel in zwei eng beieinanderliegenden Dosen verabreicht, wirksam gegen *S. haematobium*. Jedoch erweckt die niedrige Ei Reduktionsrate bei *S. mansoni* Besorgnis über eine steigende Praziquantel Toleranz.

Résumé

Introduction et objectifs : Les schistosomoses qui maintenant appartiennent au groupe des maladies tropicales négligées représentent un problème de santé publique majeur particulièrement en Afrique où sont concentrés plus de 95 % de tous les cas estimés dans le monde. Les conséquences sanitaires des schistosomoses sont considérables. En plus des complications connues dues à l'infection chronique comme l'hypertension portale, l'insuffisance rénale, le cancer et la stérilité, la schistosomose est une maladie débilitante qui est aussi responsable d'anémie, de diarrhées, de malnutrition et de douleurs abdomino-pelviennes chroniques.

En 2001, l'Assemblée Mondiale de la Santé a adopté la résolution 54.19 qui demandait instamment aux états membres de traiter régulièrement 75 % et au delà de tous les enfants d'âge scolaire et les autres groupes à risque de schistosomose. Mieux, en 2006, l'Organisation Mondiale de la Santé (OMS) a lancé sa stratégie de chimio prévention qui repose sur l'administration régulière de médicaments anti helminthiques de manière intégrée. Suite à ces appels internationaux pour l'action contre les maladies tropicales négligées, plusieurs pays africains dont le Niger ont lancé des programmes nationaux de lutte basés sur la stratégie de chimio prévention avec le soutien des partenaires.

Les objectifs de la présente thèse sont : (i) d'évaluer la morbidité de la schistosomose chez les nourrissons et les enfants d'âge préscolaire non encore inclus dans la stratégie de chimio prévention, (ii) d'évaluer la tolérance et l'efficacité du praziquantel (PZQ) selon plusieurs schémas thérapeutiques et (iii) de faire une analyse détaillée des coûts du traitement et de faire des propositions afin d'améliorer la lutte contre la schistosomose et les autres maladies tropicales négligées au Niger.

Méthodes et principaux résultats : Nous avons premièrement analysé les résultats atteints et les défis auxquels sont confrontés les trois pays d'Afrique de l'ouest (Burkina Faso, Mali et Niger) soutenus par l'initiative de lutte contre la schistosomose (SCI) en matière de lutte contre la schistosomose et les géohelminthiases. En trois ans de mise en œuvre des programmes, près de 13,5 millions de doses de médicaments ont été administrées contre la schistosomose et les géohelminthiases avec des taux de couverture variant entre 67 % et 94 %. Ces traitements au PZQ ont entrainé une réduction importante de la prévalence et de l'intensité des infections dans les sites sentinelles qui avaient été mis en place afin de suivre et

évaluer ces programmes. Les défis majeurs auxquels sont confrontés ces programmes sont leur habilité à maintenir le seuil de réduction de la morbidité obtenu et d'assurer la pérennité.

Deuxièmement, nous avons évalué la morbidité due à la schistosomose chez les nourrissons et les enfants d'âge préscolaire non encore inclus dans la stratégie de chimio prévention recommandé par l'OMS et évaluer les risques d'infection à un âge précoce. Nous avons conduit une enquête transversale dans 2 villages du Niger : Falmado, qui est endémique pour *Schistosoma haematobium* et Diambala qui est un foyer d'infection mixte *S. haematobium-S. mansoni*. Au total 282 enfants avaient été examinés (149 filles, 133 garçons, âge moyen 2,6 ans) et 224 mères (âge moyen 30,1 ans). Pour le diagnostic de *S. haematobium* deux échantillons d'urine obtenus sur 2 jours consécutifs ont été soumis à la technique de filtration urinaire standard, tandis que pour *S. mansoni*, un examen de selle selon la technique de Kato-Katz a été réalisé. A Diambala, un questionnaire a été administré aux mères afin de recueillir les données démographiques, la notion d'un traitement récent avec des antihelminthiques, l'approvisionnement en eau, l'assainissement et les pratiques de baignade de leurs enfants. La prévalence d'infection à *S. haematobium* chez les enfants et leurs mères était respectivement de 51 % et 56 % à Falmado ; et 61 % et 72 % à Diambala. La prévalence d'infection à *S. mansoni* à Diambala était de 44 % chez les enfants et 52 % chez les mères. La prévalence des infections mixtes *S. haematobium-S. mansoni* était de 29 % chez les enfants et 37 % chez les mères. Les résultats du questionnaire ont montré que 70 % mères se font accompagner par leurs enfants aux sites de transmission avant qu'ils n'aient l'âge d'un an, et que 3 quarts des mères utilisent l'eau directement prélevée des canaux d'irrigation pour laver leurs enfants.

Troisièment, nous avons évalué l'efficacité et la tolérance de deux doses de 40 mg / kg de PZQ administrées à trois semaines d'intervalle contre *S. haematobium* et *S. mansoni* chez les enfants d'âge scolaire, et la réinfection un an après. L'étude a été conduite dans 5 villages de l'ouest du Niger : Falmado, Seberi, Diambala, Namarigoungou et Libore. Nous avons procédé à trois examens parasitologiques après filtration urinaire et 3 examens de selle par Kato-Katz à chaque visite. Les enfants ont été suivis à 6 semaines, six mois et 12 mois après l'administration de la première dose de PZQ. Les réactions secondaires ont été suivies pendant un période de 4 heures suivant l'administration du PZQ par l'équipe et par questionnaire administré aux mères 24 heures après. Notre échantillon final comprenait 877 enfants infectés par *S. haematobium* ou *S. mansoni* ou les deux simultanément et qui avaient

reçus les deux doses de PZQ. Avant traitement, l'oviurie géométrique moyenne de *S. haematobium* pour 10 ml d'urine variait de 3,6 à Diambala à 30,3 à Falmado, tandis que la moyenne géométrique d'œufs par gramme (EPG) de selles pour *S. mansoni* variait de 86,7 à Diambala à 151,4 à Namarigoungou. Des réactions secondaires ont été rapportées par 33 % et 1,5 % des enfants respectivement après la première et la seconde dose de PZQ. Le taux de guérison de *S. haematobium* 3 semaines après la deuxième dose de PZQ variait entre 49 % à Falmado et 98 % à Namarigoungou avec des taux de réduction de l'oviurie allant de 92 % à 100 %. Concernant *S. mansoni*, le taux de guérison et de réduction de l'excrétion ovulaire étaient modérés, respectivement 52 % et 59 % à Diambala, 55 % et 60 % à Namarigoungou.

Quatrièmement, afin de générer plus d'évidence par rapport à la tolérance et à l'efficacité du PZQ pour la schistosomose chez les enfants d'âge préscolaire, nous avons conduit un autre essai clinique avec le PZQ sirop (Epiquantel®), chez les enfants âgés de moins de 72 mois. Cette étude a été conduite entre mai et août 2010 dans 3 villages du Niger. Au total 243 enfants infectés par *S. haematobium* et/ou *S. mansoni* avaient été traités avec du PZQ sirop à la dose de 40 mg / kg de poids après qu'un repas constitué d'une bouillie de mil leur ait été servi. Après traitement, les enfants ont été surveillés pendant une période de 4 heures et un questionnaire a été administré aux mères le lendemain afin de recueillir les réactions secondaires. Des visites de suivi consistant en 3 examens de filtration urinaire et 3 examens de Kato-Katz ont été conduites 3 et 6 semaines après le traitement. La proportion d'enfants ayant présenté des réactions secondaires précoces dans les 4 heures suivant l'administration du PQZ était de 33 % tandis que la proportion des réactions secondaires dans les 24 heures était de 6,2 %. Aucun effet indésirable grave n'a été observé. Les réactions secondaires les plus fréquentes étaient les douleurs abdominales (31 %), la diarrhée sanglante (16,2 %) et la somnolence (15,3 %). Avant traitement, 165 enfants étaient infectés par *S. haematobium* parmi lesquels 87 % avaient une infection légère (1-49 œufs pour 10 ml d'urine) et 13 % une infection sévère (≥50 œufs pour 10 ml d'urine). Le taux de guerison global à *S. haematobium* était respectivement de 86 % et 95 % trois et six semaines après traitement. Le taux de réduction de l'oviruie était quand à lui de 71 % et 77 %, respectivement 3 et 6 semaines après traitement. En ce qui concerne *S. mansoni*, 96 enfants infectés avaient été traités au PZQ. Parmi eux, 39 % présentaient une infection modérée à forte (nombre d'œufs par gramme de selle >100). Le taux de guérison était de 75 % et 50 % respectivement 3 et 6 semaines après traitement tandis que le taux de réduction de l'excrétion ovulaire était de 67 % et 19 % respectivement.

Cinquièmement, afin de contribuer à la recherche de stratégies financièrement viables pour la pérennisation des activités de lutte contre la schistosomose, nous avons conduit une étude coût-efficacité comparant la distribution de médicaments à base-scolaire et la distribution à base communautaire. Nous avions conduit cette étude en 2006 dans quatre districts afin d'estimer le coût économique du programme, le coût par traitement et le coût par infection à *S. haematobium* évité. L'étude a comparé le coût au démarrage du programme et un an après et déterminé les coûts par activités, intrants et organisation. Le coût économique total du programme incluant les dépenses spécifiques du programme, les coûts locaux et les coûts de l'appui technique international et la coordination dans les 4 districts sur la période de 2 ans était de 456 718 US$ tandis que le coût par traitement était de 0.58 US$. Le coût économique global par traitement de la stratégie à base scolaire en 2005/2006 était de 0,76 US$ tandis que le coût de la distribution à base communautaire était de seulement 0.46 US$. Si seul les coûts supportés par le programme étaient considérés, les coûts par traitement seraient respectivement de 0,47 USD pour la stratégie à base scolaire et 0,41 USD pour la stratégie à base communautaire. Dans les districts enquêtés, sur la période de 2 ans, le coût moyen par cas de schistosomose évité était de 0,76 US$ par enfant et de 6,7 US$ par adulte.

Conclusion : La pérennisation des programmes de lutte contre la schistosomose et les géohelminthiases demeure un défi important en Afrique. L'intégration avec les autres interventions de santé existantes et en particulier celles ciblant les maladies tropicales négligées et le renforcement du système de santé sont des voies pour continuer à assurer la distribution des médicaments antihelminthiques et les autres interventions. A un coût moyen de 0.58 US$ par traitement, les pays pourront l'assurer.

Une proportion importante d'enfants d'âge préscolaire est infectée par la schistosomose y compris des infections mixtes à *S. haematobium-S. mansoni.* Par conséquent, dans les zones hyper endémiques, plus d'attention doit être accordée aux enfants d'âge préscolaire et à leurs mères afin qu'ils puissent bénéficier de la chimio prévention et ainsi augmenter la couverture thérapeutique effective des personnes traitées. Le PZQ sirop est bien toléré chez les nourrissons et les enfants d'âge préscolaire. Les taux de guérison et de réduction de l'oviurie sont élevés avec *S. haematobium*. Par contre, des études complémentaires sont nécessaires afin de mieux déterminer son efficacité contre *S. mansoni*.

Chez les enfants d'âge scolaire, le PZQ administré en 2 doses rapprochées est efficace contre *S. haematobium*. Cependant les faibles taux de réduction de l'excrétion ovulaire observés suscitent l'inquiétude quant à la montée de la tolérance de *S. mansoni* au PZQ.

To my family

Agaichatou, Amina, Rakia, Kadidja, Idrissa, Salamatou, Mohamed, Hamsatou and Ada.

This thesis is dedicated to you

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1. Introduction

1.1. Schistosomiasis: biology and life cycle

Schistosomiasis is a water-related disease that is due to an infection with trematode worms, which live in the venous circulatory system of the definitive vertebrate hosts. An infection occurs through skin contact while a person is in contact with water polluted by faeces or urine of *Schistosoma*-infected individuals. An intermediate hosts (freshwater molluscs) is indispensable for the life cycle (Gryseels et al., 2006).

There are at least 19 species of schistosomes from which five species are recognized pathogenic for human, namely *Schistosoma haematobium, S. mansoni, S. intercalatum, S. japonicum* and *S. mekongi*. In sub-Saharan Africa, *S. haematobium, S. mansoni* and *S. intercalatum* occur, with the former two being the predominant species (WHO, 1993a).

Adult schistosome worms live inside the venous circulatory system. Their morphology is very similar from one species to the other. They measure 10-20 mm, the male shelters in a longitudinal gutter of a longer female worm. In the two sexes surface is roughcast protuberances. The egg contains a mobile miracidia ready to hatch. It measures 70-200 µm, depending on species. The cercariae, which measure approximately 50 µm, is characteristic by its form: the head (or body) is connected to a tail, which will enable to get rid during the penetration of the skin.

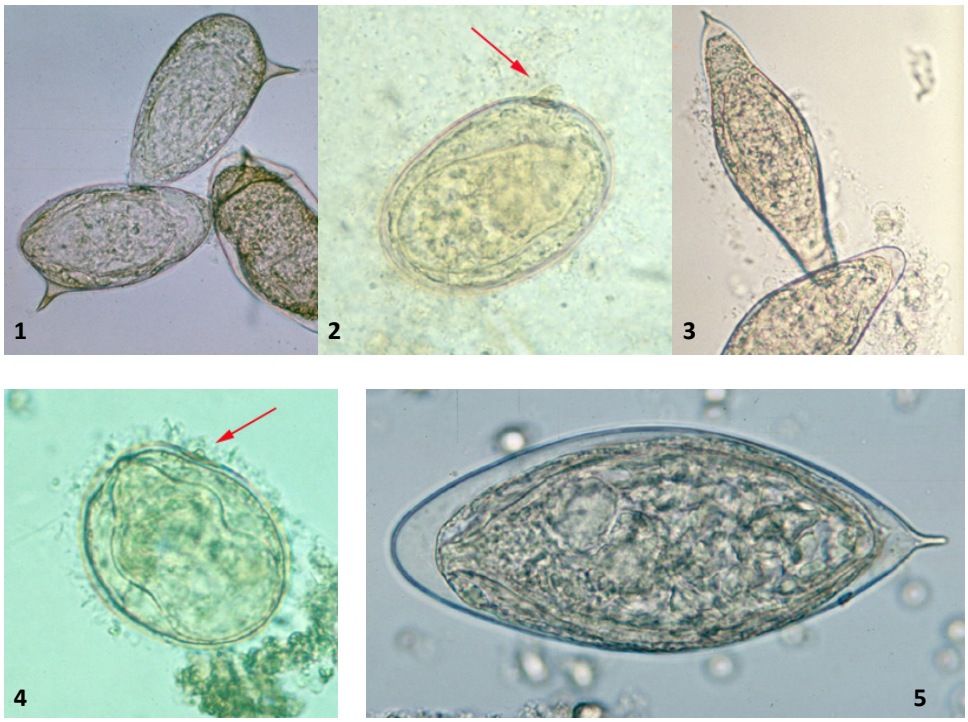

Figure 1.1. *Schistosoma* eggs: **1**. *S. mansoni* **2**. *S. japonicum* **3**. *S. intercalatum* **4.** *S. mekongi* **5**. *S. haematobium* (source: http://www.dpd.cdc.gov/dpdx; accessed: 15 August 2011)

Common characteristics of intermediate hosts are that they are freshwater gastropod molluscs, hermaphrodites and oviparous. Four species are involved in the transmission of human schistosomiasis: *Bulinus* for *S. haematobium* and *S. intercalatum*, *Biomphalaria* for *S. mansoni*, *Oncomelania* for *S. japonicum* and *Tricula* for *S. mekongi*. With the exception of *Oncomelania* that are amphibious, snails live in freshwaters, not very deep, using watery vegetation for support and food.

Bulinus species can tolerate high temperatures. A dozen species are likely to be intermediate hosts of *S. haematobium*, from which *Bulinus truncatus* is the most important African intermediate host. *Bulinus forskalii* is the usual intermediate host of *S. intercalatum. Biomphalaria* is the intermediate hosts of *S. mansoni.* These snails are more susceptible to desiccation and high temperatures compared to *Bulinus*.

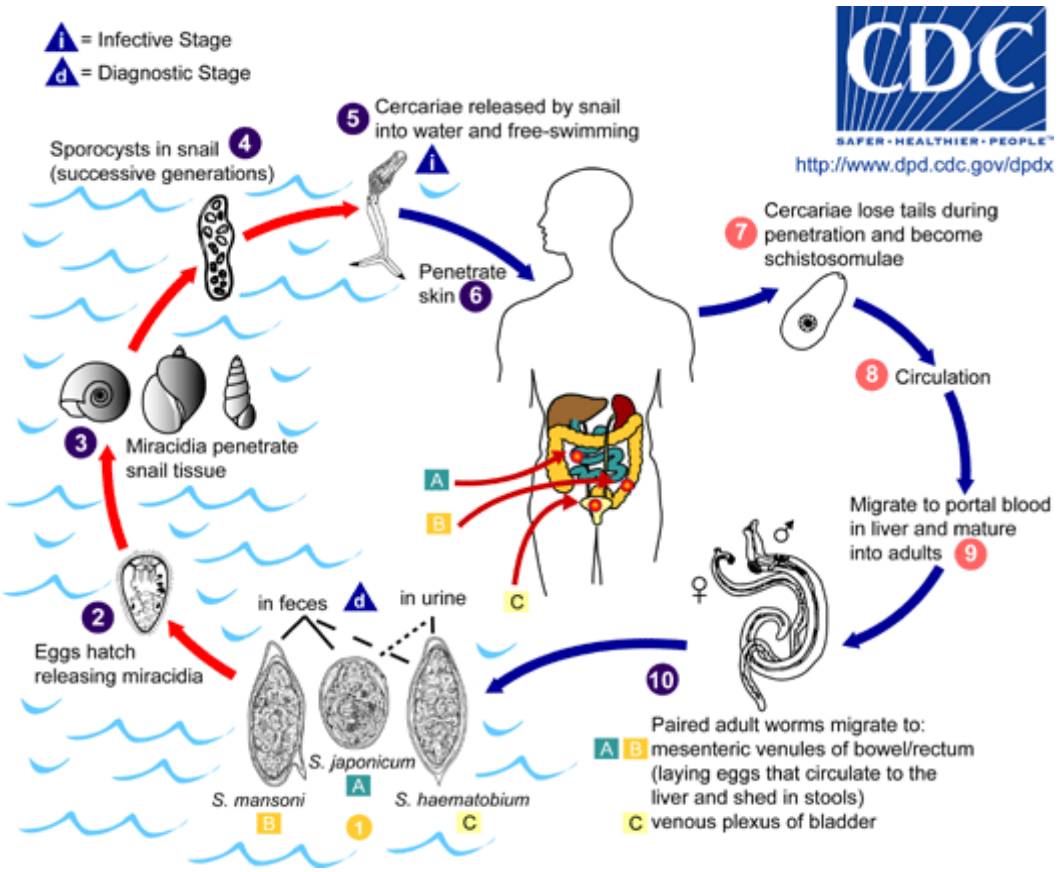

Figure 1.2. *Schistosoma* life cycle (source: http://www.dpd.cdc.gov/dpdx; accessed: 15 August 2011)

This *Schistosoma* life cycle is identical for the five human species with the only exception of the intermediate host snails. After having reached their sexual maturity in the venal system, the female worms lay their eggs in the capillaries. Eggs will have to leave the capillary and cross the organs before falling in the intestine or the bladder to be eliminated with the excreta.

It is noteworthy that for *S. japonicum*, more than 40 species of reservoir hosts exist (e.g. water buffalo and pigs), which is renders transmission control particularly challenging (Wang et al., 2008).

1.2. Schistosomiasis distribution

1.2.1. Schistosomiasis in the world

Schistosomiasis, considered as a neglected tropical disease (NTD) (Hotez et al., 2006a; Molyneux, 2004) is the most prevalent tropical disease after malaria (WHO, 1993a). Indeed, schistosomiasis is endemic in 76 countries, although transmission appears to be interrupted in several countries (WHO, 2011). It is estimates that at least 800 million people are exposed to the risk of *Schistosoma* infection in the world; among them, more than 200 million people are infected (WHO, 2011). According to estimates put forth by the World Health Organization (WHO), the number of deaths associated with schistosomiasis are approximately 300,000 people per year (WHO, 2002; van der Werf et al., 2003). Schistosomiasis is intimately connected with poverty (Hotez et al., 2006a; King, 2010). More than 90% of the people requiring preventive chemotherapy live in Africa (WHO, 2011), where 42 countries are endemic for schistosomiasis.

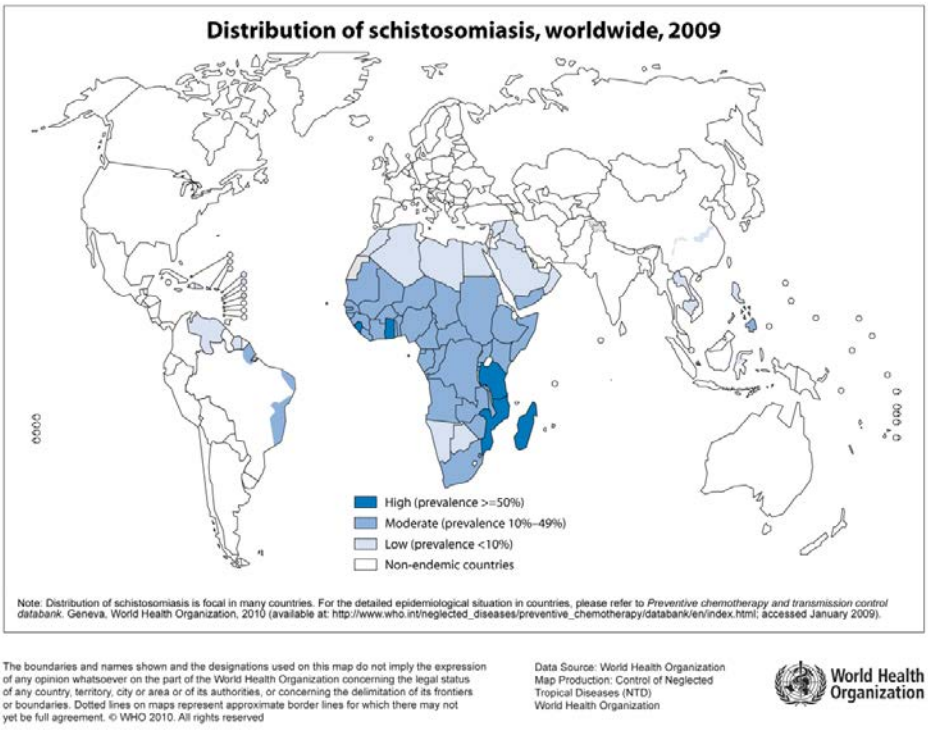

Figure 1.3. Distribution of schistosomiasis in the world in 2009 (source: WHO, 2011)

S. haematobium is distributed throughout Africa, in the valley of the Nile in Egypt, in the Maghreb region in small marshes (some remaining pockets in Algeria and perhaps in Morocco), in Madagascar and in the Middle East, Yemen (WHO, 1998b). *S. mansoni* is

widespread in Egypt, East and South Africa; in West Africa, in Latin America (Brazil and Venezuela), and in the Antilles. *S. japonicum* prevails in the People's Republic of China, in Formosa, in Indonesia and the Philippines. *S. mekongi* is endemic in Cambodia, and in Lao People's Democratic Republic. It has been eliminated in Japan and Korea. *S. intercalatum* is restricted to some parts of Central African, i.e. Gabon, Congo, Democratic Republic of the Congo and Cameroon, as well as in Angola.

1.2.2. Schistosomiasis in Niger

Schistosomiasis represents a major problem of public health in Niger. Considering the prevalence observed and the fact that the population of Niger are especially concentrated near water points, it is estimate that at least 4.5 million people are exposed to this affection on the extent of the country (Garba et al., 2006; Fenwick et al., 2009; Schur et al., 2011). The development of small dams to promote irrigation for food sufficiency in the country is the factor supporting the propagation of the disease (Ernould et al., 1999, 2004).

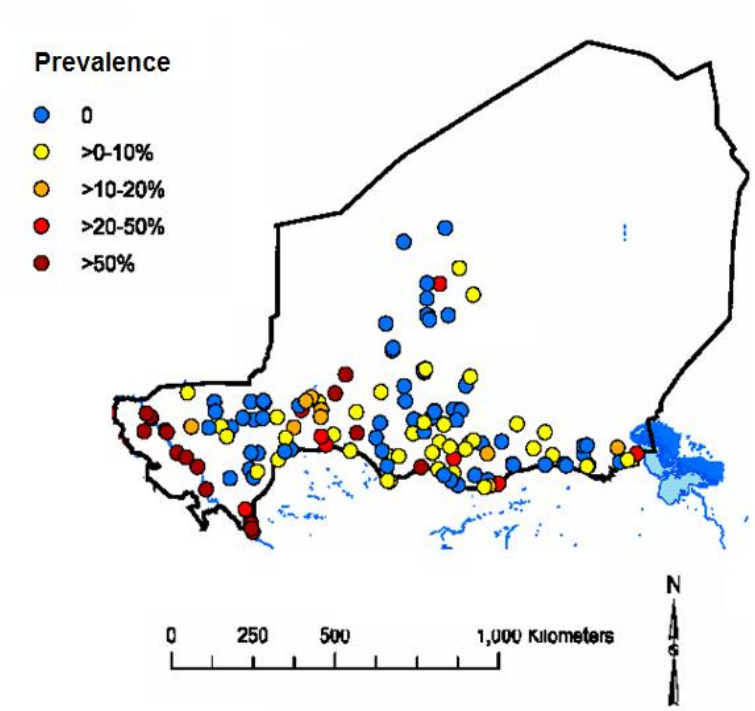

Figure 1.4. Map showing the prevalence of *S. haematobium* in Niger in 2006 (source: Clements et al., 2008)

In Niger, two forms of *Schistosoma* exist: *S. haematobium* and *S. mansoni* with however a strong prevalence of the urinary form (Garba, 2000; Garba et al., 2006).

Urinary schistosomiasis is present in all the climatic zones of the country with a high prevalence around irrigated perimeters of the Niger River, Birni Konni, Maradi and Diffa and around the temporary and permanent ponds of Téra and Mirriah and oases of the Aïr Mountains. Intestinal schistosomiasis was initially limited to the department of Gaya (Doumenge and Mott, 1987; Mouchet et al., 1988; Ernould et al., 2000; Clements et al., 2008). However, a new focus was discovered at Namarigoungou in 2002 (Labbo et al., 2003b; Garba et al., 2004b) upstream of Tillabéri on the Niger River. In the meantime, *S. mansoni* is progressing in this region replacing *S. haematobium*. The number of *S. mansoni*-endemic villages is increasing as well as the prevalence (Garba et al., 2010).

Malacologic studies carried out in Niger found the existence of many intermediate hosts. *Bulinus truncatus* has been identified as the main species responsible for the transmission of urinary schistosomiasis. *B. truncatus rothfsi* is distributed in all the climatic zones of Niger (Labbo et al., 2003a, 2008; Ernould et al., 2004), while *B. senegalensis*, even if present in all the climatic zones of Niger, is involve in the transmission of urinary schistosomiasis mainly in temporary ponds (Vera et al., 1992). *B. globosus* is found in the Niger River, the Center and the East of the country, and this snail species mainly occurs in temporary ponds. *B. forskalii*, which is distributed across the country, was found to contribute to the transmission of urinary schistosomiasis in the Niger River Valley, but at a small scale (Labbo et al., 2007). *B. jousseaumei* is localized in the Niger River Valley and *B. umbilicatus* in the extreme south of the country, in the Niger River Valley and the Center of the country but they do not transmit schistosomiasis in Niger.

Biomphalaria pfeifferi is found in the extreme south of the country (Gaya, Boboye), in Aïr mountains and recently in Tillaberi region in the Niger River Valley is responsible for the transmission of *S. mansoni* (Mouchet et al., 1988, 1990; Labbo et al., 2003b).

1.3. Morbidity due to schistosomiasis

In endemic areas, infection occurs at childhood. Infection increases in prevalence and intensity before reaching a peak around the age of 13-15 years (King et al., 1988; Verle et al., 1994). The granulomatous response to parasite eggs is responsible of the constitution of the pathology in schistosomiasis (Gryseels et al., 2006).

The miracidia secretes and excrete proteolytic enzymes diffusing through the ovular wall. Later on these ovular antigens will involve the formation of a granuloma, the elementary lesion specific of schistosomiasis disease. The formation of the granuloma translates a defensive response of the host against the aggression induced by the eggs, which cross the walls of the urinary, genital or intestinal tracts creating an ignition and bleeding. The lesions, constitute of granuloma are mainly located in the mucous membrane and under mucous membrane of the bladder, the ureter and the genitals for *S. haematobium*; of the intestine for *S. mansoni* and *S. intercalatum*. These lesions are the cause of the hypertrophy of the walls. Moreover eggs of *S. mansoni* are pulled by the blood current and can reach the liver, the lungs, the nervous system and the skin.

Clinical manifestations of schistosomiasis are classified into three phases namely (i) contamination, (ii) invasion and (iii) patent. The phase of contamination caused by the entry of cercariae into the skin begins with itching, and then appear erythematous spots, papular rash, possibly a fever and general fatigue. Most frequently this phase is quiet and unperceived.

The phase of invasion occurs after a dumb period of 2-10 weeks following the contamination. It is characterized by immune-allergic signs, such as fever, cutaneous signs (pruritus, urticaria and oedema), muscular or articular pains, cough, abdominal pains or diarrhoea.

At the patent phase, the signs cease to be univocal and depend on the territories of egg-laying of each species. It's clinically distinguishes: urogenital schistosomiasis due to *S. haematobium*, intestinal schistosomiasis due to *S. mansoni* and *S. intercalatum*, and arterio-venous schistosomiasis due to *S. japonicum* and *S. mekongi.*

1.3.1. Urogenital schistosomiasis

Haematuria is the essential and the most frequent sign. Very often it is microscopic. In certain cases, it is insufficient to draw the attention of the subject. More significant, it is final, capricious and is then repeated. Often, it is possible to observe pubic pains, descending towards the purses, even in the absence of bacterial infection; they are often revived by pain when urinating.

Pollakiuria is chronic, sometimes accompanied with burns or itching at the end of the miction. Later on, bladder and ureter granulomas can cause an obstruction of the urinary tracts, which can induce hydroureter, hydronephrosis and a renal failure; and bladder calcifications (Gray et al., 2011). These chronic bladder lesions create favourable conditions for the development of the cancer of the bladder at adult age (WHO, 1993b). Studies have shown that squamous cell bladder carcinoma are more frequent in *S. haematobium*-endemic zones (Badawi et al., 1995; O'Connor et al., 1999). The successful control of schistosomiasis led to a decrease of the number of bladder cancer in Egypt (Barocas et al., 2011).

Genital schistosomiasis, although neglected, is very frequent in the two genders. It can result, in the long-term, to sterility (Poggensee et al., 2006; Nayama et al., 2007).

In women the main signs of the low genital organs are vulvo-vaginal and cervical lesions leading to external tumours of the vulva, pain and bleeding during sexual intercourse and menstruation disorders. The specific lesion at the colposcopy is the “sandy patches” (HellingGiese et al., 1996). In the upper genital organs, schistosomiasis can cause miscarriage, ectopic pregnancy, tubal obstruction and sterility. These bleedings due to schistosomiasis would create favourable situation for the transmission of HIV (Feldmeier et al., 1994, 1995; Hotez et al., 2009; Stoever et al., 2009). These genital lesions can sometimes also be found in *S. mansoni* infections (Lambertucci et al., 2009; Cavalcanti et al., 2011). In men, the main signs are epididymitis, funiculitisis, spermato-cystitis, prostatitis, haemospermia and painful erections (Feldmeier et al., 1999; Leutscher et al., 2000).

1.3.2. Intestinal schistosomiasis

Intestinal schistosomiasis is due to *S. mansoni* and *S. intercalatum* and *S. japonicum.* The eggs are mostly localized in the ramifications of the portal system, which explains the topography of the lesions: intestine, liver and spleen.

The symptoms are not specific and not always present. Most of the time, the diagnosis is carried following a systematic parasitological examination of the stools. The most frequent signs are diarrhoea, sometimes bloody, dysenteries, alternating sometimes with the constipation, splenomegaly and hepatomegaly.

The hepatosplenic lesions are very frequent in *S. mansoni* infection and less in *S. intercalatum.*

The main long-term complication is the liver fibrosis which induces a portal hypertension which can lead to ascitis, oesophageal varices, variceal bleeding and death (van der Werf et al., 2003; Gray et al., 2011).

Anaemia, fatigue, low cognitive capacities are signs of the subtitle morbidity due to schistosomiasis (King and Dangerfield-Cha, 2008).

Schistosomiasis lesions treated at a young age regress quickly and the clinical symptoms disappear (Boisier et al., 1998; Campagne et al., 2001; Vennervald et al., 2005). However, in case treatment is delayed until adulthood, it was shown that its effects are weak, especially on the portal fibrosis (Richter, 2003). Sandy patches the female genital schistosomiasis pathognomonic sign do not regress after treatment with praziquantel (Kjetland et al., 2006). These observations underscore that it is necessary to implement treatment of children before irreversible lesions have occurred.

1.4. Diagnostic of schistosomiasis

1.4.1. Clinical diagnostic

In urinary schistosomiasis, the diagnosis is generally evoked in the presence of haematuria. In *S. mansoni*, the diagnosis is generally considered by the presence of bloody diarrhoea or dysentery.

The clinical diagnosis remains useful and is more specific in the case of the urinary schistosomiasis than in the intestinal form.

1.4.2. Parasitological diagnostics

It is based on the presence *Schistosoma* eggs in the urine (*S. haematobium*) or in the stool (other *Schistosoma* species) by using parasitologic techniques.

Urine filtration technique on Nucleopore, Nytrel or paper allows a quantification of the results and appears the most interesting method in the field for the diagnostic of *S. haematobium.*

The Kato-Katz technique of thick faecal smears under rectangle of cellophane (Katz et al., 1972) is recommended for the diagnosis of *S. mansoni*, *S. japonicum* and *S. intercalatum.*

The sensitivity of these techniques can be improved by examining multiple samples (Campagne et al., 1999; Utzinger et al., 2001; Kosinski et al., 2011), which remedy day-to-day variation of egg output (Engels et al., 1996).

Formalin-based techniques for sedimentation or concentration can also be used. The Flotac (Knopp et al., 2009a, 2009b) is another technique which appeared interesting in the diagnosis of schistosomiasis and STH (Cringoli, 2006; Utzinger et al., 2008). However, the Flotac technique, although more sensitive to detect light infections (Glinz et al., 2010), appears to be more complex and costly (Speich et al., 2010).

1.4.3. Immunological diagnosis

The most promising technique is the circulating cathodic antigen (CCA) dipstick (Stothard et al., 2009) which detects antigens of *Schistosoma* in the urines. CCA is more sensitive and indicated in the screening for *S. mansoni* (Standley et al., 2010; Shane et al., 2011). The sensitivity of CCA is low in detecting *S. haematobium* infection (Erko et al., 2008; Stothard et al., 2009). Other techniques using blood or of urines specimens exist, like blood soluble egg antigen-enzyme-linked immunosorbent assay (SEA-ELISA), eosinophil cationic protein (ECP), (Leutscher et al., 2008; Stothard et al., 2009; Webster et al., 2010), but they are not used in routine and sometime, they do not distinguish between active and past infection.

1.4.4. Other diagnostic methods

Radiological techniques can show the lesions induced by schistosomiasis. In addition to the traditional X-ray, ultrasonography since the beginning of the 1980s became the field most suitable technique for schistosomiasis-related morbidity assessment (Hatz et al., 1992a, 1992b; Hatz, 2001; Koukounari et al., 2006). The availability of portable machines as well as

its reliability, its acceptance by the patients, and the possibility to examine many people are major features of this technique for morbidity studies. It has largely contributed to epidemiological research on the description of the lesions due to schistosomiasis and in the definition of the treatment strategies and periodicity (Devidas et al., 1989; Hatz et al., 1998; Wagatsuma et al., 1999; Campagne et al., 2001; Garba et al., 2004a).

Biopsy of the rectal mucous membrane followed by the examination of the fresh specimen on the microscope has a great sensitivity but it does not allow any quantification and cannot be used in the field.

Figure 1.5. Image showing some current diagnostic techniques❶. Macrohematuria, ❷. Dipstick for microhematuria, ❸. CCA test ❹. SEA-ELISA test

1.4.5. Community diagnostic

It determines endemicity of schistosomiasis in a community and consequently the treatment strategy to apply in this community according to the prevalence. It consists in surveys using school-aged children samples. The prevalence found is used to classify the community in a level of endemicity according to WHO thresholds (WHO, 2006). The techniques used for the surveys are parasitology, but also methods known as rapid assessment techniques are used.

The three most widely used rapid assessment techniques for community diagnostic of urinary schistosomiasis are: (i) school-based questionnaires, (ii) visual haematuria and (iii) reagent strip testing for microhaematuria detection in the urine.

Lengeler and colleagues developed and validated a simple school-based questionnaire approach, which proved useful in identifying high-risk communities of urinary schistosomiasis at the district level in Tanzania (Lengeler et al., 1991a, 1991b, 1991c). This method, initially developed in the Kilombero district, then successfully validated in the nearby Kilosa district, was subsequently validated in several African countries (N'Goran et al., 1998; Utzinger et al., 2000b; Lengeler et al., 2002). Good correlations were found between schoolchildren's answers regarding the question "did you have blood in urine in the last 2 weeks" (Lwambo et al., 1997; Booth et al., 1998; Guyatt et al., 1999). In Côte d'Ivoire, N'Goran *et al.* showed that the use of questionnaire was rapid and cost-effective to identifiy schools at highest risk of urinary schistosomiasis (N'Goran et al., 1998).

Visual haematuria technique is also easy to perform. Fresh urine specimens are examined in a transparent container. However, in adults and girls, this indicator can be less sensitive because of a higher frequency of urinary infections that are not related to schistosomiasis and menstruations. The use of reagent strips allows identifying the non visual haematuria. They have been used for the validation of the results obtained by questionnaire in Tanzania and in Côte d'Ivoire (N'Goran et al., 1989). However the diagnostic accuracy of urine dipsticks varied according to the brands used (Ugbomoiko et al., 2009). They are particularly interesting within the framework of the evaluation of schistosomiasis morbidity after a treatment campaign. However, they would be less useful in the zones of weak prevalence (Robinson et al., 2009; Kosinski et al., 2011).

Considering the increasing needs for mapping in the new control programmes launched in sub-Saharan Africa (Brooker et al., 2009; Standley et al., 2009; Baker et al., 2010), at country level, and of the significant costs required, lot quality insurance sampling (LQAS) techniques (Brooker et al., 2005) seem an attractive alternative to reduce cost and save time. It has been used in *S. mansoni* survey in Uganda and shows a good applicability and speed in the survey.

1.5. Schistosomiasis control

1.5.1. Preventive chemotherapy

In highly endemic areas (e.g. sub-Saharan Africa), control of schistosomiasis rests on morbidity control, which is implemented through preventive chemotherapy (PCT) or mass drug administration (WHO, 2006). Other control strategies include health education for behaviour change, safe water, improved sanitation and snail control. PCT has been endorsed by WHO as the global strategy because of the safety, efficacy and low costs of praziquantel. Importantly, PCT has a rapid impact on morbidity (Molyneux, 2004; Molyneux et al., 2005; Hotez, 2009). In addition, this strategy advocate for co-implementation of neglected tropical diseases instead of single disease control because of the rapid impact of the treatments on health and cost-effectiveness considerations (Molyneux, 2004; Molyneux et al., 2005; Hotez et al., 2006b; Kolaczinski et al., 2007; Hotez, 2009). Monitoring surveys undertaken after large-scale implementation of this strategy confirms rapid and drastic reduction in the morbidity level of schistosomiasis (Kabatereine et al., 2007; Koukounari et al., 2007; Toure et al., 2008; Zhang et al., 2008). However, these programmes mainly depend on external funds in sub-Saharan Africa, and hence sustainability remains a great concern as well as increasing resistance of the population to repeated rounds of treatment (Parker et al., 2008; Allen and Parker, 2011).

Several international initiatives have been put in place over the past several years demonstrating renewed interest in schistosomiasis research and control. The most important initiatives are summarized in Table 1.1. Moreover, funding for implementation of PCT has increased considerably, thanks to support by the World Bank for schistosomiasis control in Yemen and USAID. Drug manufacturers also contribute with free donation of medicine (http://www.who.int/neglected_diseases/pharma_contribution/en/index.html; accessed on 24 August 2011). In addition to the well known mectizan and albendazole donation programme for lymphatic filariasis elimination and the zithromax donation for trachoma elimination, new initiatives of free drug donation have been recently launched, such as mebendazole (200 millions tablets/year by Johnson & Johnson) and albendazole (400 million tablets/year by Merck) for STH control in school-aged children through Children Without Worms (CWW), and 200 million (20 million/year) tablets of praziquantel donation from Merck Serono by 2017.

The World Health Assembly resolution 54.19, adopted in 2001, urges member states to treat at least 75% of all school-aged children who are at risk of schistosomiasis before 2010. Data assembled by WHO in 2009 show that this goal is far from being reached because of many constrains. In fact, only 19.6 million people were treated in the endemic regions, representing 8.2% of the estimate people infected, even if an increase of 116% was observed compared to 2006 (WHO, 2011). It should be noted, however that this report concern only 21 endemic countries out of the 42 in Africa. The constrains in implementing the PCT strategy are the insufficient commitment of the countries and consequently low in-country funds allocated, and the availability of drugs (Fenwick, 2009; Savioli et al., 2009; Hotez et al., 2010).

Table 1.1. Major organizations supporting research and implementation of schistosomiasis control in sub-Saharan Africa

Name (creation year)	**Countries of intervention**	**Objectives**	**Leading organizations**	**Funding source**
SCI (2002) Schistosomiasis Control Initiative http://www3.imperial.ac.uk/schisto	Burkina Faso Mali Niger Tanzania Uganda Zambia	-To encourage development of sustainable schistosomiasis and STH control programmes -To reach at least 75% of school-aged children and other high-risk groups with chemotherapy -To create a demand for sustained schistosomiasis and STH control. -To promote access to anthelminthic drugs and good case management in the regular health system. -To develop a rigorous monitoring and evaluation plan	Imperial College of Science and Technology, London	Bill & Melinda Gates Foundation
CONTRAST (2006) A multi-disciplinary alliance to optimise schistosomiasis control and transmission surveillance in sub-Saharan Africa http://www.eu-contrast.eu/	Cameroon Kenya Uganda Niger Senegal Tanzania Zambia	Research for control focused on: -molecular tools for new insight into snail-schistosome transmission biology; -characterisation of schistosome-snail relationships and transmission potential; -spatial epidemiology for schistosomiasis risk mapping and prediction; -social sciences approaches to better understand and encourage local control interventions; -outreach and dissemination facility established;	University of Copenhagen Partners DBL NHM-UK ICL Swiss TPH Coris Bioconcept	European Union
SCORE (2008) Schistosomiasis Consortium for Operational Research and Evaluation http://score.uga.edu	Côte d'Ivoire Ethiopia Kenya Mozambique Niger Tanzania Uganda	-Evaluation of alternative approaches to mass drug administration (MDA) in communities with high and moderate prevalence rates of schistosomiasis; -Studies related to subtle morbidity, snail infections and schistosome population genetics; -Elimination of schistosomiasis in a defined geographic area and providing data and insights into effective strategies for moving large areas from having a low prevalence of infection to eliminating schistosomiasis. -Field evaluations of CCA urine assay for use as a screening tool for *S. mansoni* -Research and evaluation on human diagnostic tests for schistosomiasis	University of Georgia, Athens, GA, USA	Bill & Melinda Gates Foundation
ICOSA (2010) Integrated Control of Schistosomiasis and Intestinal Helminths in Sub-Saharan Africa	Côte d'Ivoire Liberia Malawi Mozambique Niger Tanzania Uganda Zambia	-To provide a total of 75 million treatments for schistosomiasis and soil-transmitted helminths over a 5 year period -To provide support to continue to scale-up towards national coverage control of these infections To assist old programmes to move towards a long-term sustainable strategy for disease control.	- SCI, Imperial College of Science and Technology, London - Centre for Neglected Tropical Diseases (CNTD)	DFID

1.5.2. The move towards elimination

Once morbidity control has been achieved, the next logical step is elimination of the disease as a public health problem. This can be envisaged in areas where sustainable control has led to low endemicity (WHO, 2002). Experiences in several countries and the disease infection indicators decrease in response to chemotherapy (Utzinger and de Savigny, 2006; Kabatereine et al., 2007; Koukounari et al., 2007) has shown that it is an achievable goal in sub-Saharan Africa (Laamrani et al., 2000; Knopp et al., 2011). A schistosomiasis elimination programme was launched on 28 July 2011 in Zanzibar. The objectives of this project, funded by the Bill & Melinda Gates Foundation through the University of Georgia project named SCORE are to eliminate schistosomiasis as a public health problem in Unguja Island in 3 years and to eliminate transmission in 5 years in Pemba (http://score.uga.edu/Elimination.html).

Mass drug administration and additional measures such as strengthening of the health system, improvement of sanitation, health education for behaviour change, safe water, (Curtale et al., 2010; Gray et al., 2010), snail control (Takougang et al., 2007) and reinforcement of the surveillance (Amarir et al., 2011) are necessary for sustainable schistosomiasis control. Indeed, investment in schistosomiasis control is a waster if benefits after successful PCT campaigns are not sustained after such rapid impact interventions.

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2. Goals and objectives

2.1. Aim of the study

The goals of this PhD thesis in Epidemiology are (i) to deepen our understanding of the epidemiology of and morbidity due to schistosomiasis in young children; and (ii) to evaluate the efficacy of praziquantel and to assess the economic cost implication of mass drug administration strategies in order to enhance the control of schistosomiasis control in sub-Saharan Africa.

2.2. Specific objectives

- To elucidate the objectives and the organisation of the schistosomiasis and soil-transmitted helminthiasis control programmes in selected West African countries.
- To present the results achieved and the impact of mass drug administration campaigns undertaken in selected West African countries in 3 years since the establishment of large-scale schistosomiasis and soil-transmitted helminthiasis control programmes.
- To discuss the challenges West African countries now face in ensuring sustainability of schistosomiasis control, and thus consolidating achievements made to date.
- To determine the financial and economic costs of the national schistosomiasis and soil-transmitted helminthiasis control programme in Niger, particularly the cost per person treated and the cost per *Schistosoma* infection averted.
- To determine the cost-effectiveness of a school-based and community-based preventive chemotherapy strategy in Niger.
- To determine the prevalence and intensity of schistosomiasis in children below the age of 5 years and in their mothers in a village in Niger where only *S. haematobium* occurs, and in a village where *S. haematobium* and *S. mansoni* co-exist.
- To enhance our understanding of the epidemiology of schistosomiasis and risk factors for an infection in early childhood.
- To evaluate the safety and efficacy of praziquantel syrup (Epiquantel®) in *Schistosoma* infection in infants and preschool-aged children in three endemic villages of Niger.
- To assess the efficacy and safety of two closely spaced doses of praziquantel against *S. haematobium* and *S. mansoni* infection among school-aged children in a highly endemic area of Niger and to describe reinfection patterns over a 1-year period after treatment.

3. Present and future schistosomiasis control activities with support from the 'Schistosomiasis Control Initiative' in West Africa

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Running title: Progress of schistosomiasis control in West Africa

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3.1. Summary

Since 2004 the West African countries of Burkina Faso, Mali and Niger are implementing national schistosomiasis and soil-transmitted helminthiasis (STH) control programmes with financial and technical support from the 'Schistosomiasis Control Initiative' (SCI). In the first three years of the control programmes, nearly 13.5 million of people have been treated with praziquantel against schistosomiasis and albendazole against STH with coverage rates varying between 67.0% and 93.9%. These treatments have resulted in a reduction of the prevalence and intensity of *Schistosoma* infection in the sentinel cohorts that were set up to monitor and evaluate the national control programmes. The challenges currently facing by these national control programmes are the ability to maintain the reduction in morbidity achieved thus far due to the mass treatment campaigns and ensuring sustainability. For reinforcement of surveillance monitoring the establishment of a geographical information system is suggested in order to contribute towards enhanced sustainability of these programmes. Our new working hypothesis is that targeted control accompanied by periodic mass treatment campaigns (every two to three years) can contribute to maintaining the low levels of morbidity achieved thus far. The implementation of integrated neglected tropical disease control programmes in these countries will provide means to ensure the financial sustainability of control activities for the years to come.

Key words: schistosomiasis control, morbidity, integration, sustainability, Burkina Faso, Mali, Niger.

3.2. Introduction

Schistosomiasis represents a significant public health problem in tropical and sub-tropical areas. A recent analysis suggests that 779 million people are at risk of schistosomiasis, and 207 million people were infected in mid-2003 throughout the world (Steinmann *et al.* 2006). Africa is the continent that is suffering the most with an estimated 85% of those currently exposed living on this continent (WHO, 1999; Chitsulo *et al*. 2000; Steinmann *et al.* 2006).

Apart from the known long-term complications of a chronic Schistosoma infection (e.g. portal hypertension, kidney failure, bladder cancer and sterility), schistosomiasis is a debilitating disease leading to anaemia, malnutrition, chronic abdominal and pelvic pain, and diarrhoea; all which are underestimated with regards to schistosomiasis related morbidity (King *et al.* 2006). A recent re-assessment of the morbidity due to schistosomiasis (King *et al.* 2005) emphasised that the true burden of the disease, as expressed in disability-adjusted life years (DALYs) lost, is between 2% and 15%, contrary to the former estimates of the World Health Organization, which quantified the burden due to schistosomiasis at only 0.5-0.6% (WHO, 2002).

Following World Health Assembly (WHA) resolution 54.19, several African countries established national programmes to control morbidity due to schistosomiasis and soil-transmitted helminthiasis (STH). Burkina Faso, Mali and Niger, in West Africa, were selected to benefit from financial and technical support of the 'Schistosomiasis Control Initiative' (SCI; http://www.sci-ntds.org) and large-scale schistosomiasis and STH control programmes have been established (Fenwick *et al.* 2006). The main strategies employed by these national control programmes are the organization of mass treatment campaigns and targeted health education in areas where prevalence rates justified the intervention using WHO (2002) criteria.

This article summarizes some of the key results obtained in the three years since the establishment of these large-scale schistosomiasis and STH control programmes in 2004 in the three West African countries supported by SCI. Finally, the challenges the countries now face in ensuring sustainability and thus consolidating the achievements made will be discussed, including proposal for integrating multiple neglected tropical disease control programmes.

3.3. National schistosomiasis control programmes in Burkina Faso, Mali and Niger

3.3.1. Distribution of the disease

Schistosoma haematobium is the most widespread species in all three West African countries (Garba *et al.* 2006). The transmission areas are primarily irrigation schemes, along rivers, and near both temporary and permanent water ponds. *Schistosoma mansoni* is less prevalent compared to *S. haematobium*, and is limited to certain irrigated areas such as the Office of Niger, Bandiagara, Selingué and Baguinéda-Koulikoro in Mali (Koukounari *et al.* 2006). In Mali, the prevalence of *S. mansoni* exceeds 50% in the Office of Niger. In Burkina Faso, *S. mansoni* is localised in the south-western part of the country; while in Niger transmission sites are primarily in the Niger River valley, but prevalence is increasing along the river where an emergent foci has been reported recently (Garba *et al*. 2004).

3.3.2. Objectives, targets and strategies of control programmes

In line with WHA resolution 54.19, the goal of the national control programmes is to reduce schistosomiasis morbidity to a level at which it will not constitute a public health problem. Hence, the three programmes have endorsed the WHO objective of reaching at least 75% of the school-aged children, and have added the objective of targeting high-risk communities with the drug of choice, praziquantel (Doenhoff *et al.* 2009). Two drug distribution strategies have been used by the programmes. The first distribution strategy is through the schools where trained teachers or health workers distribute the drugs to school-aged children. The second drug distribution strategy used is community-based, where trained drug distributors selected by the community, trained teachers or health workers treat community members.

3.4. Mass treatment and its impact

In the three countries, nearly 13.5 million of people have been treated in a 3-year period starting in 2004. The coverage rates of the mass treatment in the different study areas varied between 67.0% and 93.9% (Table 3.1). The lack of accurate population statistics due to a high rate of migration in certain areas of Niger might explain the somewhat lower coverage rate

observed in Niger. Difficulties with the mass treatment campaigns were experienced mainly in large urban areas where populations were reluctant to comply with the treatment despite the significant number of people at risk in these towns such as the capital cities of Bamako and Niamey (Dabo *et al.* 2003; Labbo *et al.* 2003). Interestingly, this was observed particularly among more educated population strata. The regions were gradually integrated in the mass treatment campaigns. In both Burkina Faso and Niger the mass treatment campaigns have been scaled up to target all regions; however, in Mali, the endemic areas of the centre and eastern part of the country still remain to be covered by mass treatment.

Table 3.1. Reported number of people treated with praziquantel and average coverage rates in the study regions during the first three years of schistosomiasis control activities implemented in Burkina Faso, Mali and Niger

	2004			2005			2006			Total		
	No. of regions	**No. of people treated**	**Coverage (%)**	**No. of regions**	**No. of people treated**	**Coverage (%)**	**No. of regions**	**No. of people treated**	**Coverage (%)**	**No. of regions**	**No. of people treated**	**Coverage (%)**
Burkina Faso	4	1,027,007	92.1	9	2,278,615	89.6	4	2,818,578	93.9	13	6,124,200	93.0
Mali				4	2,598,138	93.5	2	472,257	89.3	6	3,070,395	92.8
Niger	3	671,670	68.0	5	2,034,510	67.0	5	1,540,556	84.9	8	4,246,736	72.8
Total		1,698,677			6,911,263			4,831,391			13,441,331	

For monitoring and evaluation purposes, cohorts of school-aged children in all three countries, and adolescent and adult cohorts in Niger were recruited and followed to monitor the impact of mass drug distribution campaigns. In Mali, repeated cross-sectional surveys of adolescent and adults were also carried out. In addition rapid prevalence assessment surveys using questionnaires have been conducted in Niger. The cohorts were examined before treatment each year. They were treated after baseline data collection and were re-treated once a year in their respective localities at the time of the mass treatment campaigns to ensure the effect of the mass drug administration could be measured. Table 3.2 shows the results of the cohort who completed the 3 years surveys as well as the cross-sectional surveys at the 3 time points of study. Following two distribution campaigns, a decline in both prevalence and most importantly intensity of schistosome infections was observed in all the three countries (Table 3.2). The initial schistosome prevalence was higher in the school-aged group than in either the adolescent or the adult groups. In Burkina Faso the most dramatic reduction in prevalence of infection was observed among the school-aged population group; i.e. the baseline infection prevalence of 59.6% in 2004 dropped to 6.2% in 2005 and to 7.7% in 2006. In Mali, the decrease of observed prevalence was satisfactory; from 71.4% at baseline to 36.4% and 28.3% after the first and second treatment rounds, respectively. However, in high transmission areas where the initial prevalence of infection was high, the remaining prevalence after two treatment rounds was still almost 50%. The effect of the treatment on intensity of *S. haematobium* infection in Mali was a reduction from 73.1 eggs/10 ml urine to 7.6 eggs/10 ml urine and 5.6 eggs/10 ml urine one and two years after baseline screening, respectively. We believe that in addition to the immediate health improvements of those treated, the benefit of the two treatments in the school-aged population will continue into adulthood (Ouma *et al.* 2005; King, 2006).

Table 3.2. Prevalence and intensity of infection in children cohorts, adolescent and adult longitudinal and cross-sectional data pre- and post-treatment

	Baseline			Year 1 follow-up			Year 2 follow-up		
Children	**No. of individuals examined**	**Prevalence (95% CI)**	**Mean infection intensity* (95% CI)**	**No. of individuals examined**	**Prevalence (95% CI)**	**Mean infection intensity (95% CI)**	**No. of individuals examined**	**Prevalence (95% CI)**	**Mean infection intensity (95% CI)**
Burkina Faso	783	59.6 (56.2-63.1)	94.2 (76.4-111.9)	783	6.2 (4.5-7.9)	1.0 (0.2-1.9)	783	7.7 (5.8-9.6)	6.8 (1.6-11.9)
Mali	1399	71.4 (69.0-73.8)	73.1 (63.3-82.8)	1399	36.4 (33.9-38.9)	7.6 (6.1-9.1)	1399	28.3 (25.9-30.7)	5.6 (3.1-8.1)
Niger	1145	75.4 (72.9-77.9)	58.7 (48.6-68.8)	1145	37.4 (34.6-40.2)	8.6 (6.4-10.8)	1145	35.7 (32.9-38.5)	13.9 (10.5-17.5)
Adolescent and adults									
Mali (cross-sectional data)**	197	54.8 (47.9-91.6)	15.3 (10.1-20.5)	847	41.1 (37.8-44.4)	9.4 (6.8-12.1)	534	9.7 (7.2-12.3)	0.4 (0.2-0.6)
Niger (longitudinal data)	116	24.1 (16.3-31.9)	2.2 (1.6-3.8)	116	9.5 (4.1-14.8)	0.2 (0.0-0.6)	116	11.2 (5.4-16.9)	0.7 (0.1-1.3)

* arithmetic mean; ** At baseline adolescents and adults have contributed data from 7 communities in Segou while at follow-up visits different people from 10 communities in Segou were recruited in these studies.

3.5. Maintaining the benefits of mass treatment

3.5.1. The continuation of the treatment campaigns

Two mass treatment campaigns do not resolve the health problems due to schistosomiasis. Several areas in the three West African countries still remain to be covered by mass treatment campaigns. This is due to the significant resources necessary to scale up control activities. Moreover, re-treatment is essential to keeping morbidity at low levels. The treatment of the target populations is of primary importance and must continue.

The continuation of the mass treatment campaigns relies heavily on the need for free and/or donated drugs. SCI provided the drugs for free mass drug administration. However apart from the mass treatment campaigns the delivery of praziquantel is through the cost recovery system in the countries. In addition, SCI supported registration of several praziquantel manufacturers in the countries in order to encourage competitive bidding process which would obtain best prices during the in-country procurement process (Garba *et al.* 2006). But even with the reduction of the price of praziquantel (Savioli *et al.* 2004), its cost still remains high for the budget of these three national governments and for the current cost recovery system. International initiatives with pharmaceutical companies, like the ivermectin, albendazole and the azithromycin donation programmes are essential. There is a fear of donor fatigue if a praziquantel donation programme is not established and if national governments are unable to contribute to the costs of distribution. Gabrielli *et al*. (2006) showed that mass drug distribution campaigns only cost US$ 0.32 per person treated (cost of the drug, management, planning, training, social mobilization and remuneration of distributor included).

There is also a need to reinforce the capacities of the district health staff to ensure all the control activities at their level are successfully programmed and conducted with coordinated workshops in planning, surveillance and evaluation. In addition, it is necessary to increase the manpower of the district health staff with qualified personnel. This option may be difficult for these three West African countries in the context of Word Bank structural adjustment policies, which require a reduction of the number of government agents.

One suggestion is for community structures or associations made up of the high-risk groups (e.g. gardening associations, fishermen groups, rice growers and women co-

operations) to take the responsibility of the treatment under the supervision of the health workers. Drugs must be available at all levels of the health structure in order to treat individual cases free of charge. These both assume a general motivation of the target populations and a reinforcement of the existing community structures like the health committees, the irrigation scheme management committees, and other local non-governmental organizations (NGOs) and associations. In particular, the village communities need to be responsible for the management of their health centres. Enhancing school health programmes is another way to regularly distribute drugs and such programmes could possibly permit more periodic treatment campaigns (every two to three years). Integration with other health activities could also reduce the costs and therefore encourage governments and partners to contribute to the financing of mass treatment campaigns.

3.5.2. Villages targeted for control

Due to the fact that schistosomiasis is focal (Labbo *et al.* 2008; Ernould *et al*. 2004), monitoring of control activities requires more precise annual evaluations, primarily at the village level. Such precise evaluations permit the monitoring of the long-term impact and effectiveness of the mass treatment campaigns and a possible reduction in the transmission. A reinforcement of local capacities in monitoring and evaluation is essential at all levels. It is misleading to think that a national coordination team alone can carry out all necessary surveys. This would take too much time and would require a very high data management capacity to ensure rapid analysis in order to formulate treatment strategies in a timely manner. Moreover, the district health staffs do not have the capacity or the autonomy to undertake the control programmes and to conduct the surveillance activities. Even when district level capacities exist, health agents have additional work and therefore the activities required for schistosomiasis control are difficult to achieve.

Analysis of results indicates that the risk of reinfection is associated with the location of the village, the age of the individual and haematuria, but is not associated with the sex of the individual or the frequency of water contact (Satayathum *et al.* 2006; King, 2006). Thus a schistosomiasis control strategy targeted at village level seems the most logical and the establishment and use of a geographical information system (GIS) platform can assist the national programmes in targeting villages that require control interventions and defining

overall treatment strategies (Simoonga *et al.* 2009; Clements *et al.* 2008), but its role may be limited in resource poor countries.

3.5.3. Additional control strategies

The transmission of schistosomiasis is linked with behaviour. Long-term information, education and communication (IEC) campaigns could increase the knowledge of the populations, and thus contribute to behaviour change (Poggensee *et al.* 2005). Safe water supplies, and the construction and use of latrines, must be provided or improved (Singer and Castro, 2008; Asaolu and Ofoezie, 2003). It is important to remember that schistosomiasis is primarily found in poor communities and in countries with very limited resources. In addition, preventing children from bathing in infested water when temperatures reach above 40°C will always be difficult. Therefore, it would be deceptive to think of obtaining a good coverage of both safe water supplies and latrines in a short period. Thus, an increase in education and poverty reduction efforts are necessary for the control of schistosomiasis.

3.5.4. Can we consider transmission control?

Molluscicides were not used by any of the control programmes in West Africa probably due to cost and the fear of ecological consequences (Sturrock, 2001). Considering the weak impact of the mass treatment campaigns on the transmission (King, 2006), the use of molluscicides in small temporary ponds where fishing activities are not practised can be considered on a small scale (Sturrock, 2001) to contribute to transmission control. This will ensure the reduction of transmission and therefore will enable the control programmes to adopt a more periodic treatment schedule. Using molluscicides in these small and temporary ponds where fishing activities are absent can therefore be advantageous to national control programmes. A study in northern Cameroon (Tagougang *et al*. 2006) showed that in the sahelian zone where temporary ponds represent the main transmission system for schistosomiasis a reduction in snail population without causing ecological damage to fish and other claming plates is possible if 4 fold less the recommended dose (0,25mg/m3) of molluscicides is applied twice. The reduction of the molluscicide dose is more cost efficient, but cost effectiveness studies are still necessary.

3.6. Future: Integration of the programmes and the control of neglected tropical diseases

The integration of vertical control programmes is considered as a cost effectiveness way to deliver a health package (Lammie *et al*. 2006; Brady *et al*. 2006). The American government (United States Agency for International Development) awarded a $100m USD grant for the integrated control of neglected tropical diseases to the company Research Triangle International (RTI). Burkina Faso, Mali and Niger are among the selected fast-track countries for implementation of this neglected tropical disease control project. This integration will concentrate on delivery of appropriate treatments against schistosomiasis, STH, trachoma, lymphatic filariasis and onchocerciasis. The main strategies of the integration plan are mass drug distribution, IEC and training. This grant offers the three countries a chance to have continued support to their national control programmes, but for how long is still a question.

Integration with other existing health activities is another way to ensure the continued distribution of the drugs. In Niger, an integrated distribution of the polio vaccination and mebendazole for children under 5 was successfully completed in December 2006 when three million children were successfully treated against intestinal worms. Though the under 5s are not considered in the WHO recommendations for schistosomiasis control (Stothard and Gabrielli, 2007), they represent a significant proportion of those affected (Bosompem *et al*. 2004), and therefore integration of schistosomiasis control with existing health activities, such as national immunisation days could be a channel to reach this target.

3.7. Conclusion

The long-term treatment of target populations in an integrated and decentralized way, and a progressive introduction of transmission control, are essential for the successful fight against schistosomiasis in Africa. The poverty reduction policy of increasing school attendance and providing safe water would ensure populations are more aware of the disease and therefore reduce reinfection rates.

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4. Schistosomiasis in infants and preschool-aged children: infection in a single *Schistosoma haematobium* and a mixed *S. haematobium-S. mansoni* foci of Niger

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4.1. Abstract

The burden of schistosomiasis in infants and preschool-aged children and their mothers is poorly known. We carried out a cross-sectional epidemiological survey in two villages in Niger: Falmado is endemic for *Schistosoma haematobium* only, whereas a mixed *S. haematobium*-*S. mansoni* focus has been reported from Diambala. The survey examined 282 children (149 girls, 133 boys, average age: 2.6 years) and 224 mothers (average age: 30.1 years). For *S. haematobium* diagnosis, two urine samples obtained on consecutive days were subjected to the standard urine filtration method. Additionally, macro- and microhaematuria were determined. The diagnosis of *S. mansoni* was based on a single stool sample with duplicate Kato-Katz thick smears. In Diambala, a standardised, pre-tested questionnaire was administered to mothers, which recorded demographic data, treatment history with anthelminthic drugs, household sanitation and water supply, and bathing practices for their children. Prevalence of egg-patent *S. haematobium* infections among young children and their mothers was respectively 50.5% and 55.6%, in Falmado, and 60.5% and 72.2% in Diambala. The prevalence of *S. mansoni* infection in Diambala was 43.8% among children and 52.1% in mothers. Mixed egg-patent infections of *S. haematobium* and *S. mansoni* were revealed in 28.6% of the children and 37.3% of the mothers. Questionnaire data showed that 69.8% of the children were accompanied by their mothers to schistosomiasis transmission sites before they were one year of age, and that three-quarter of the mothers used water directly drawn from the irrigation canals to wash their children. To conclude, a substantive proportion of children below the age of five years had egg-patent schistosomiasis, inclusive of co-infection with *S. haematobium* and *S. mansoni*. In the context of schistosomiasis control, more attention should be paid on preschool-aged children and women of childbearing age, so that they can benefit from preventive chemotherapy, which in turn might increase effective coverage of those infected.

Keywords: Schistosomiasis, *Schistosoma haematobium*, *Schistosoma mansoni*, co-infection, infants, preschool-aged children, women, prevalence, Niger

4.2. Introduction

Classified among the neglected tropical diseases (NTDs) (Molyneux et al., 2005; Hotez et al., 2006), schistosomiasis remains one of the most important parasitic diseases in the tropics and subtropics, and constitutes a major public health problem (van der Werf et al., 2003; Steinmann et al., 2006). Schistosomiasis is endemic in Niger, with 3-4 million people exposed, the majority of whom have *Schistosoma haematobium* infections (Garba and Aboubacar, 2000), but there are recent signs that *S. mansoni* is expanding along the Niger River Valley (NRV), probably due to water-resource developments (Steinmann et al., 2006). The main sites of transmission are the irrigated areas of the Niger River and the semi-permanent and permanent ponds (Labbo et al., 2008). Following the World Health Assembly (WHA) resolution 54.19 put forth in May 2001 (WHO, 2002), Niger is implementing a national schistosomiasis and soil-transmitted helminthiasis control programme with the support of the Schistosomiasis Control Initiative (Garba et al., 2006, 2009; Fenwick et al., 2009). The objective of this programme is to reduce morbidity due to schistosomiasis and soil-transmitted-helminthiasis by treating at least 75% of all school-aged children and other high-risk communities where the prevalence exceeds 50% with praziquantel and albendazole, a strategy termed 'preventive chemotherapy' (Savioli et al., 2004; Garba et al., 2006, 2009).

By focusing treatment upon the school-aged population, WHA resolution 54.19 neglected children of preschool age, thus preventing them from benefiting from the praziquantel treatment given to their older peers, and hence creating a potential health inequity (Johansen et al., 2007; Stothard and Gabrielli, 2007). Root causes include the belief that very young children would not yet been exposed to infested freshwater bodies, thus an insufficient understanding and documentation of the extent and severity of schistosomiasis in this age class, and a paucity of pharmacokinetic safety data of praziquantel among young children (Allen et al., 2002; Geary et al., 2010). However, in endemic zones, women are frequently accompanied by their children, even at young age, when they go to ponds, rivers or irrigation canals, all of which may be contaminated with cercariae, the infective stage to humans. Therefore children are likely to come into contact with contaminated water at a very young age. Recent studies in Nigeria (Mafiana et al., 2003; Opara et al., 2007), Ghana (Bosompen et al., 2004) and Uganda (Odogwu et al., 2006) have shown that infection with *S. haematobium* and *S. mansoni* can indeed occur in very early childhood.

The present study pursued two objectives. First, to determine, the prevalence of schistosomiasis in children below the age of five years and in their mothers in a village where only *S. haematobium* occurred, and in a village where both *S. haematobium* and *S. mansoni* were present. The second objective was to enhance our understanding of the epidemiology of schistosomiasis and risk factors for an infection in early childhood. The results reported here shed new light on a largely neglected issue of schistosomiasis epidemiology and control and may therefore assist public health experts and disease control managers to devise adequate strategies to tackle the disease in the preschool-aged population and their mothers.

4.3. Materials and methods

4.3.1. Study area

This cross-sectional epidemiological study was carried out in Diambala and Falmado, in the Western Sahel zone of Niger, in April 2007 (Fig. 4.1). The two villages have been selected after a survey in school-aged children has shown a high prevalence of schistosomiasis. Diambala (geographical coordinates: 14.313 N latitude; 1.300 W longitude) is located in the NRV in the department of Tillabéri, near an irrigated rice zone. The estimated population at-risk of schistosomiasis in this department is 193,825 people. Falmado (12.514 N latitude; 2.861 W longitude) is located in the department of Birni Gaouré in the valley of Dallol Foga, surrounded by permanent and temporary ponds with an at-risk population of 148,833 individuals.

An exhaustive door-to-door census conducted prior to parasitological and questionnaire surveys revealed a total population of 3,961 in Diambala and 676 inhabitants in Falmado. In Diambala, the major schistosomiasis transmission sites are the irrigation canals and the seven temporary ponds where favourable conditions enable the intermediate host snails to thrive. It is a well-known focus of mixed *S. haematobium* and *S. mansoni* and anthelminthic drugs have been administered prior to our study. In Falmado, rains occurring during the wet season ensure that both the permanent and temporary ponds surrounding the village are filled up, facilitating transmission of schistosomiasis. However, prior to the present study, the village of Falmado was never targeted for either praziquantel or albendazole treatment. We proceeded to an exhaustive sampling of all the households having a child of less than five years after census to participate to the study.

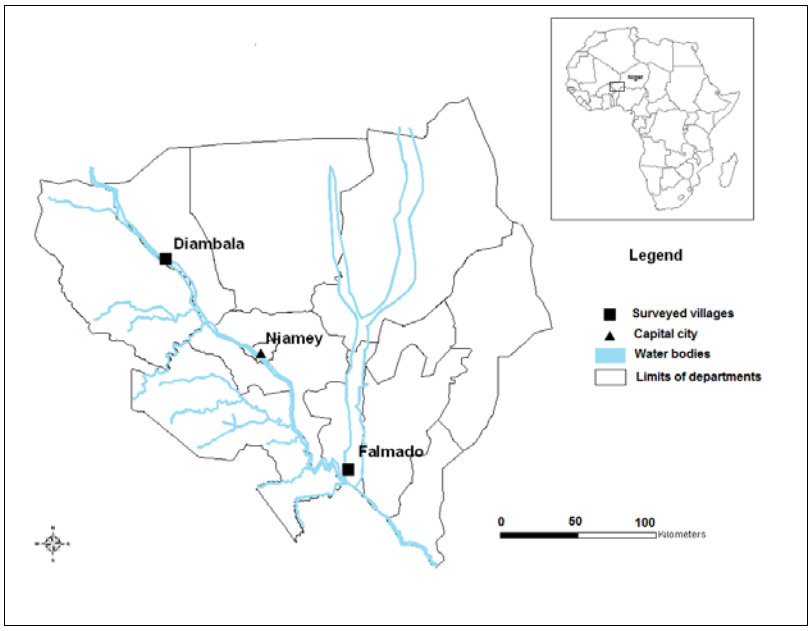

Fig. 4.1. Map of the study area in western Niger.

4.3.2. Ethical consideration and treatment

Ethical clearance was obtained from the Niger National Ethical Committee (Niamey, Niger) and from the NHS-LREC review board of St Mary's Hospital, Imperial College (London, UK) application 03.36. In the field, the objectives of the study were explained to the local village chiefs and political and religious authorities who gave their consent to conduct the study.

All the mothers with children under five years of age were invited to participate in the study. The objectives, procedures and potential risk and benefits were explained prior to data collection. Once the mothers gave their oral informed consent (illiteracy rate is very high, hence we opted for oral rather than written informed consent), their children were included in the study. The whole population of the two villages were treated immediately after the study with praziquantel (single 40 mg/kg oral dose) and albendazole (single 400 mg oral dose), using crushed tablets for the youngest children by the national schistosomiasis and soil-transmitted helminthiasis control programme during their mass treatment campaign. Praziquantel and albendazole tablets were crushed between two spoons, diluted with water and given to the child by the mother generally accustomed to give drugs in this way to their children. Drugs administered in this way were well tolerated.

4.3.3. Questionnaire survey

A questionnaire assessing risks for early childhood schistosome infections was administered to participating mothers in Diambala, the village characterized by a mixed focus of *S. haematobium* and *S. mansoni*. We employed a standardized, pre-tested questionnaire that has been successfully used before (Beidou, 2006) in the local language (Zarma) by trained field investigators. Socio-demographic data (e.g. age, sex, profession and educational attainment), knowledge and attitude towards water contact patterns, means of prevention, water supply, availability of latrines, and recent history of treatment with anthelminthic drugs were collected.

4.3.4. Parasitological survey

Urine collection containers (and in Diambala also stool collection containers) with unique identifiers were handed out to the participating mothers and their young children. Each subject included in the study underwent two parasitological examinations of their urine on consecutive days. For the collection of the urine samples, from a few very young children, plastic potties were given out to facilitate collection of urine. Urine specimens were collected between 10:30 and 14:00 hours and the standard urine filtration method was employed (WHO, 1985). In brief, urine samples were vigorously shaken, and 10 ml were filtered using nucleopore filters. The filters were placed on a microscope slide, a drop of Lugol's iodine was added and the slides were examined under a microscope by experienced laboratory technicians. The number of *S. haematobium* eggs per slide were counted and recorded for each individual separately. Additionally, urine specimens were examined for macrohaematuria (visible blood in urine). Only the first day urine sample was subjected to microhaematuria testing, using Hemastix® strip (Bayer; Leverkusen, Germany).

A single stool specimen collected from participating mothers and their young children in Diambala was subjected to the Kato-Katz technique (Katz et al., 1972) with duplicate thick smears prepared from each sample. We also recorded the consistency of stools (liquidity and presence of blood). Other intestinal parasites detected under the microscope were also recorded.

We classified intensity of schistosome infections according to guidelines put forth by the World Health Organization (WHO, 2002). For *S. haematobium*, we determined between light

infection (1-49 eggs/10 ml of urine), and heavy infection (≥50 eggs/10 ml of urine). The intensity of *S. mansoni* infection was classified into light infection (1-99 eggs per gram of stool (EPG)), moderate infection (100-399 EPG) and heavy infection (≥400 EPG).

4.3.5. Statistical analysis

All data were entered into an Excel spreadsheet, transferred into EpiInfo version 6.04d (Centers for Disease Control and Prevention; Atlanta, USA) and analysed with the latter software. We calculated the various proportions of interest and made comparisons using the Pearson χ^2 test, or the Yates' corrected χ^2 test, as appropriate. For statistical significance, we use a threshold of 5%.

4.4. Results

4.4.1. Characteristics of study population

Table 4.1 summarises the demographic characteristics of the studied population, stratified by village. Overall, 282 children and 224 mothers participated in the study. The average age of the whole surveyed preschool-aged children group was 2.6 years with a standard deviation (SD) of 1.1 years. There were more girls than boys in both villages with a sex ratio of male to female of 0.89. The age of the mothers ranged from 15 to 50 years, with an average of 30.1 (SD=8.6) years.

In Diambala, 97.8% of the surveyed children had a history of treatment with albendazole and 1.1% had a history of treatment with praziquantel. Almost three quarters of the mothers (72.3%) reported to have previously received praziquantel. In Falmado, no previous treatment was reported with either drug, neither in mothers nor in children.

Table 4.1: Characteristics of the study population in the two villages of Diambala and Falmado in western Niger and prior treatment history with praziquantel and albendazole.

Characteristics	**Village**		**Children (< 5 years)**	**Mothers**
Number of participants (%)	Diambala	Male	84 (45.4)	
		Female	101 (54.6)	
		Total	185 (100)	143
	Falmado	Male	49 (50.5)	
		Female	48 (49.5)	
		Total	97 (100)	81
	Total	Male	133 (47.2)	
		Female	149 (52.8)	
		Total	282 (100)	224
Mean age (SD)	Diambala		2.7 (1.0)	31.4 (8.7)
	Falmado		2.6 (1.2)	27.8 (7.9)
	Total		2.6 (1.1)	30.1 (8.6)
History of treatment with praziquantel in % (95% CI)	Diambala		1.1 (0.1-3.9)	72.3 (64.2-79.5)
	Falmado		0.0 (0.0-3.7)	0.0 (0.0-4.4)
History of treatment with albendazole in % (95% CI)	Diambala		97.8 (94.5-99.4)	0.0 (0.0-2.6)
	Falmado		0.0 (0.0-3.7)	0.0 (0.0-4.4)

4.4.2. Infection with S. haematobium

Table 4.2 summarises the results of *S. haematobium* infection in both children aged below five years and their mothers. The prevalence of *S. haematobium* among children was 60.5% in Diambala and 50.5% in Falmado. There is no difference between girls and boys ($\chi^2 = 0.01$, $P = 0.9$). The prevalence of heavy infection of *S. haematobium* (≥50 eggs/10 ml of urine) was 6.2% in the children of Falmado. The prevalence of macrohaematuria and microhaematuria among preschool-aged children was respectively 5.2% and 50.5% in Falmado, and 2.2% and 38.9% in Diambala. The prevalence of both macrohaematuria and microhaematuria was higher in Falmado compared to Diambala, but the difference was not statistically significant ($\chi^2 = 1.00$, $P = 0.316$ for macrohaematuria; $\chi^2 = 3.49$, $P = 0.061$ for microhaematuria).

Among mothers, the prevalence of *S. haematobium* was 55.6% in Falmado and 72.2% in Diambala. The prevalence of heavy infection was particularly high in Falmado (8.6%). The prevalence of macrohaematuria and microhaematuria among mothers was respectively 8.6% and 61.7% in Falmado, and 2.1% and 52.4% in Diambala.

Table 4.2. Prevalence of *S. haematobium* infection and morbidity indicators among children aged below 5 years and their mothers in the two study villages of Diambala and Falmado, western Niger.

Characteristics	Village	n	Children (< 5 years)	n	Mothers
S. haematobium infection prevalence in % (95% CI)					
	Diambala	185	60.5 (53.1-67.6)	143	72.2 (64.2-79.4)
	Falmado	97	50.5 (39.2-59.8)	81	55.6 (44.1-66.6)
Prevalence of heavy *S. haematobium* infections (≥50 eggs/10 ml of urine) in % (95% CI)					
	Diambala		0.0 (0.0-1.9)		0.0 (0.0-2.5)
	Falmado		6.2 (2.3-13.0)		8.6 (3.5-17.0)
Mean (SD)					
	Diambala		4.3 (6.3)		6.8 (7.69)
	Falmado		9.4 (31.2)		12.9 (28.9)
Macrohaematuria in % (95% CI)					
	Diambala		2.2 (0.6-5.4)		2.1 (0.4-6.0)
	Falmado		5.2 (1.7-11.6)		8.6 (3.5-17.0)
Microhaematuria in % (95% CI)					
	Diambala		38.9 (31.8-46.3)		52.4 (43.9-60.8)
	Falmado		50.5 (40.1-60.8)		61.7 (50.2-72.3)

4.4.3. Infection with S. mansoni

The results of the infection with *S. mansoni* and other intestinal parasites in Diambala are presented in Table 4.3. Overall, the prevalence of *S. mansoni* was 43.8%. There was no statistically significant difference in infection prevalence among boys and girls. 17.3% of the children presented light infections (1-99 EPG), 23.8% moderate infections (100-399 EPG), whereas 2.7% of the children were heavily infected (≥400 EPG). The proportion of both liquid stools and blood in stool was 3.2%.

In the mothers group, the prevalence of *S. mansoni* was 52.1%. Stratification by infection intensity revealed 13.4%, 29.6% and 9.2% light, moderate and heavy infections, respectively. The macroscopic characteristic of the stools from the mothers showed that 18.3% contained blood and that 2.1% were liquid.

Table 4.3. Prevalence and intensity of *S. mansoni* infection, other helminth infections and stool consistency in children below the age of 5 years and their mothers in the village of Diambala, western Niger.

Characteristics	Children (< 5years)	Mothers
Number of individuals examined	185	143
Prevalence of *S. mansoni* in % (95% CI)	43.8 (36.5-51.3)	52.1 (43.6-60.6)
Prevalence of mixed infection with *S. mansoni* and *S. haematobium* in % (95% CI)	28.6 (22.3-35.7)	37.3 (29.4-45.8)
Mean infection intensity in EPG (SD)	80.7 (132.6)	151.4 (263.5)
Infection intensity classes in % (95% CI)		
No infection	56.2 (48.7-63.5)	47.9 (39.4-56.4)
Light infection (1-99 EPG)	17.3 (12.1-23.5)	13.4 (8.3-20.1)
Moderate infection (100-399 EPG)	23.8 (17.8-30.6)	29.6 (22.2-37.8)
Heavy infection (≥400 EPG)	2.7 (0.9-6.2)	9.2 (5.0-15.1)
Liquid stools in % (95% CI)	3.2 (1.2-6.9)	2.1 (0.4-6.0)
Blood in stool in % (95% CI)	3.2 (1.2-6.9)	18.3 (12.3-25.7)
Enterobius vermicularis in % (95% CI)	8.6 (5.0-13.7)	2.8 (0.8-7.0)
Hookworm in % (95% CI)	2.7 (0.9-6.2)	4.9 (2.0-9.9)
Hymenolepis nana in % (95% CI)	0.0 (0.0-1.9)	2.1 (0.4-6.0)

4.4.4. Co-infection with S. haematobium *and* S. mansoni

In Diambala, more than a quarter (28.6%) of the preschool-aged children was co-infected with *S. mansoni* and *S. haematobium*. The respective prevalence of co-infection with both *S. mansoni* and *S. haematobium* among mothers was 37.3%.

4.4.5. Risks factors for early childhood schistosome infections

Table 4.4 summarises the results obtained with the questionnaire administered to the mothers in Diambala. The mothers knew about schistosomiasis, its symptoms, and the role of water contact in the transmission of the disease. Fig. 4.2a shows that the irrigation canal, which is the main water contact site for villagers, was also the principal source of water utilized by the women. The availability of latrines in the households was low (18.9%), and hence open defecation ("in the bush") was practiced by four out five of the villagers (Fig. 4.2b).

Most of the mothers (69.8%) stated they brought infants younger than one year of age to the irrigation canal (Fig. 4.2c), thus children were put in contact with the transmission sites very early in their life. The water of the canal was used by 75.3% of the mothers to wash their children, while the water from the well or drilling was used by only 30.2% of the women (Fig. 4.2d). As shown in Fig. 4.2e, three-quarter of the mothers said that they washed their children

directly in the canal (Fig. 4.3), and 51.3% said they used a bucket for bathing (Fig. 4.4). With the exception of one mother, all reported to use soap while washing their children (Fig. 4.2e).

Table 4.4. Mothers' knowledge and awareness of schistosomiasis in Diambala, western Niger (number of mothers interviewed = 147)

Knowledge and awareness	Positive responders (%)
Know about schistosomiasis	142 (96.6)
Know a place where one becomes infected	142 (96.6)
Know that schistosomiasis is a water-related disease	135 (90.5)
Know at least one symptom of schistosomiasis	140 (95.5)

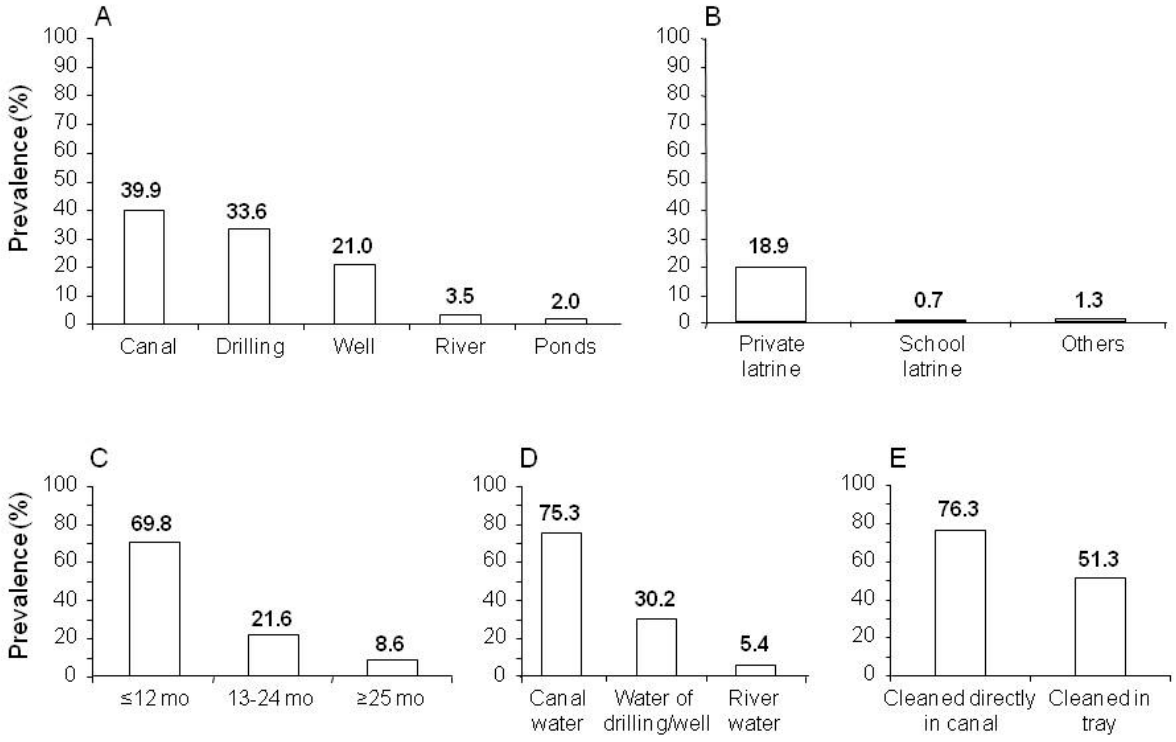

Fig. 4.2. Frequency in % of (A) water sources used by the mothers; (B) disposal sites of the human excreta; (C) age of the infants at first exposure to contamination sites; (D) water used to clean infants and preschool-aged children; and (E) cleaning practices of the infants by the mothers.

Fig. 4.3. A mother with her 1-year and 3-year-old children in the canal in Diambala, western Niger.

Fig. 4.4. A young mother bathing their child in a small bucket, while older children are playing in the pond.

4.5. Discussion

This epidemiological survey in the western part of Niger has revealed that children below the age of five years are at significant risk of schistosomiasis. Moreover, it is also evident that in one of the two study villages presenting as a mixed infection focus of *S. haematobium* and *S. mansoni*, young children have contracted both forms of schistosomiasis. Our study population consisted of 282 infants and preschool-aged children, and their mothers (n = 224). To our knowledge, this is the largest study carried out to date for investigation of schistosomiasis among infants and preschool-aged children. In previous studies, Perel and colleagues (1985) examined 142 preschool-aged children also in Niger, Odogwu and co-workers (2006) studied 136 young children in Uganda, whereas Mafiana et al. (2003) examined 209 young children, and Opara et al. (2007), another 126 preschool-aged children in Nigeria. Furthermore, our findings showed that co-infection with both *S. haematobium* and *S. mansoni* already occurs at very young age, since more than a quarter of the surveyed infants and preschool-aged children in Diambala were co-infected, an issue that has been neglected thus far.

While we found a prevalence of *S. haematobium* of 50.5% and 60.5% in Falmado and Diambala, respectively, and a prevalence of 43.8% for *S. mansoni* in Diambala in our group of young children in western Niger, prevalence ranging from 3.9% to 71.8%, and from 7% to 47.4% were found for *S. haematobium* and *S. mansoni*, respectively, in the other settings (Perel et al., 1985; Mafiana et al., 2003; Bosompen et al., 2004; Odogwu et al., 2006; Opara et al., 2007; Sousa-Figueiredo et al., 2008). It should be noted that the prevalence of *S. mansoni* reported by Odogwu et al. (2006) in Uganda was 47.4%, however this was only after carrying out a total of six Kato-Katz thick smear readings (three stool samples with duplicate Kato-Katz examinations), while only a duplicate Kato-Katz examination was conducted in our study using a single stool sample. Furthermore, the Odogwu et al. (2006) study consisted of a sample size of only 19 preschool-aged children where such exhaustive confirmatory parasitological examinations were undertaken, with the remainder of the child cohort examined by single Kato-Katz but bolstered with urine-circulating cathodic antigen (CCA) rapid diagnostic test. Without doubt, we would have found a higher prevalence if we had carried out several Kato-Katz examinations on multiple stool samples, coupled with urine-CCA tests. Hence the true *S. mansoni* prevalence in our study might be considerably higher than reported here, because of the lower sensitivity of a duplicate Kato-Katz thick based on a single stool sample when compared to multiple Kato-Katz thick smears obtained from

multiple stool samples (de Vlas and Gryseels, 1992; Utzinger et al., 2001; Booth et al., 2003; Bergquist et al., 2009).

The high prevalence of *S. mansoni* both among young children and their mothers in Diambala reflects the expansion of intestinal schistosomiasis in the NRV upstream from Tillabéri. The intermediate host snail of *S. mansoni*, *Biomphalaria pffeiferi*, was found in five out of eight irrigated areas (Namarigoungou, Diambala, Bonféba, Toula and Daikaina) surveyed upstream and in the surrounding area of Tillabéri (Labbo et al., 2003). A previous investigation by Garba et al. (2004) found human infection with *S. mansoni* only in the village of Namarigoungou where a prevalence of 5.9% was observed. This constitutes a major health risk for the local population, which might be further exacerbated once the Kandadji dam construction is completed as noted before (Hunter et al., 1993; Tecsult, 2006). The Kandadji dam is located 187 km upstream of Niamey on the Niger River and the construction commenced in August 2008. The area for which major environmental, health and social impacts are predicted extends over approximately 4,500 km². The dam itself will be an earth embankment with a length of 8.78 km and a peak height of 231 m. The water surface is estimated at 282 km^2 extending over a length of 60 km. The dam will be used for hydropower production (565 GWh) and irrigated agriculture (31,000 ha). Impoundment of the water reservoir will result in forced resettlement of approximately 35,000 people. The micro-climate, which will result from the dam lake, will probably lead to an increase in the distribution area and the number of *B. pfeiferi*. Moreover, the migration phenomenon brought on by the arrival of workers for the dam construction and the forced resettlement of resident population, and also the introduction of new irrigated areas will increase the number of people at risk and those who will become infected (Lerer and Scudder, 1999; Steinmann et al., 2006).

Urinary schistosomiasis is highly endemic in the two villages studied here. Indeed, the prevalence of *S. haematobium* in each village exceeded 50%, the threshold recommended for large-scale administration of praziquantel (WHO, 2002). To our knowledge, our study is the first to highlight such a high prevalence of *S. haematobium* in children below the age of five years in Niger. In a previous study conducted by Perel and colleagues (1985) in the village of Liboré (located near an irrigated zone of the Niger River) and in the village of Zarmeye (located near a temporary pond), a prevalence of 14.1% and 4.6%, respectively was found.

In a study in Ghana, Bosompen et al. (2004) found a prevalence of 11.2% among children aged 2 months to 5 years with the youngest infected child only four months old, as assessed

by the urine sediment method. This technique is known to be less sensitive than urine filtration used in our study. By employing an immunological test, Bosompen and colleagues (2004) found a prevalence of 30% in the same study population. In a previous study carried out in Niger, the youngest infected child was six months old (Perel et al., 1985), as in the current study. In Nigeria, Opara et al. (2007) found a prevalence of 19.8% and Mafiana et al. (2003) found a prevalence of 71.8% in children younger than 5 years. The high prevalence observed in our study highlight the intense transmission of urinary schistosomiasis in the NRV. We did not observe a statistically significant difference between the prevalence according to age, even though previous studies showed infection may start at a very early age (Perel et al., 1985; Bosompen et al., 2004).

Detection of 50 or more *S. haematobium* eggs per 10 ml of urine is regarded as an indicator of risk for morbidity, as is macrohaematuria (WHO, 2002), which is used by several control programmes as an indicator for the monitoring and for the identification of endemic communities warranting treatment. In Diambala, although the prevalence of infection was high, we did not find any heavily infected children or macrohaematuria. On the other hand, in Falmado, 6.2% of the children were heavily infected and 3.2% had macrohaematuria. This reveals that not only can the prevalence of *S. haematobium* be very high in the children below five years of age, but also that they can be heavily infected and therefore are at risk of developing morbidity very early in life. In Ebonyi Benue River Valley of Nigeria, Anosike et al. (2003) found a prevalence of 27.6% in children younger than five years. The children also had a very high mean arithmetic eggs count of 298.4 per 10 ml of urine. The high *S. haematobium* prevalence that we found in Falmado can be explained by the intensive transmission and by the fact that the village was never subjected to praziquantel administration prior to our study.

In mothers of Diambala, the overall prevalence of *S. mansoni* was 52.1%. The prevalence of moderate infection and heavy infection were 29.6% and 9.2%, respectively. This reflects the high morbidity in women of childbearing age and justify the extension of large-scale drug administration campaigns to this target by WHO (Allen et al., 2002; Ajanga et al., 2006; Friedman et al., 2007).

The overall prevalence of *S. haematobium* in mothers was 72.2% in Diambala, constituted by only light infections. The absence of heavy infection intensities is probably due to the impact of the previous mass treatment campaigns carried out by the national

schistosomiasis control programme. Mass treatment campaigns with praziquantel and albendazole, targeting all school-aged children and the total population in highly endemic areas, have been carried out in NRV in 2004 and 2005. Children under five years of age were treated with albendazole during integrated deworming and poliomyelitis vaccination campaigns in December 2006 for Falmado and March 2007 for Diambala with estimated coverage rates in excess of 90%.

Since the main objective of the national schistosomiasis control programme is to control morbidity, it can therefore be concluded that a significant reduction of morbidity was obtained in the treated areas. In Falmado, a village that had not been targeted during the mass treatment campaigns, the prevalence of *S. haematobium* was 55.6% with a prevalence of 8.6% being heavy infections.

In high schistosomiasis transmission areas, infants would be exposed to the risk of obvious infection, especially if they accompany their mothers to transmission sites or if they bathe regularly. In Diambala, 99.3% of the mothers questioned provided information on water contact related to their domestic activities and the exposure of their children to the risks of transmission. The proportion of mothers with a latrine in their house was low (17.7%), therefore the majority of human waste was disposed outside the village, in the bush and temporary ponds. The water of the irrigation canals was used for domestic activities by two-third of the mothers. In our study the majority of the mothers (76.7%) were accompanied by their children to the canal or the pond and washed them with the contaminated water. Mothers brought their children with them because they did not have suitable guardian to watch over the children while they conducted their daily activities or because they planned on bathing their children in a bucket (51.8%) or directly in the water (52.8%) once their activities were complete.

Bosompem et al. (2004) observed that 29.2% of the mothers wash their children directly in the irrigation canal. In our study the average time that a child spent in the water was 15 min (SD = 8 min). Our results are comparable with those of Odogwu et al. (2006) in Uganda where 71.4% of the mothers confirmed washing their children with lake water for an average duration of 28 min (SD = 15 min), hence considerably longer than in our study. Exposure time for the children when they accompanied their mothers was a determining factor in the transmission of schistosomiasis infection and its severity. The high rates of prevalence and intensity of infection found in school-aged children, the reason for which they are the priority

target of most control programmes, results from the fact that the infection accumulates from an early age. Due to this behaviour, school-aged children in hyperendemic zones are likely to develop severe clinical signs of schistosomiasis if they are left untreated. The harmful behaviour of the mothers with respect to not preventing their children from coming in contact with infested water could be explained by their ignorance of schistosomiasis prevention and transmission although in Diambala our results show that 90% of the mothers were aware that schistosomiasis is a water-related disease. Hence, it is possibly that the lack of accessible clean water combined with the necessity of taking their infants with them when performing their household chores could explain the persistence of such risk associated behaviour.

The use of soap, although claimed by the majority of the mothers, did not seem to be convincing with regard to impeding cercariae from penetrating the unbroken skin. During our study, we observed mothers placing their children into the canals or in buckets for long periods of time for the children to play and the mothers to conduct their daily activities. The amount of time the children were in the contaminated water was largely sufficient for the child to become infected.

In conclusion, the present study revealed the extent of *S. mansoni* and *S. haematobium* (co)infection in children aged less than five years in two hyper-endemic villages in Niger and highlights these infections as an important, yet neglected public health issue for schistosomiasis control. As *S. mansoni* is spreading in the NRV in the hydro-electric Kandadji dam area, it is conceivable that schistosomiasis in younger children will continue to increase, and thus to more accurately monitor and assess this issue, additional surveys are urgently needed to confirm and better quantify this geographical zone of infection. It is important to note that there is a persistence of risky behaviours within the study populations. More than 80% of the women had no access to latrines and therefore disposed of their waste in nature and two-third of the women used the irrigation canals for both their water supply and to wash their children. We noticed a positive impact of the prior praziquantel administration on morbidity as the number of light infections was higher and in addition no severe infection was found in mothers in treated zones. This indicates that the high infection responsible for gross morbidity is preventable through regular treatment. Because of the safety of praziquantel, women of childbearing age should be given this drug during mass treatment campaigns and also on a routine basis in maternal health clinics. It is imperative that a system to determine where children of young age are heavily infected and then these children aged less than five

years should be treated during mass treatment campaigns in order to reduce or prevent the development of morbidity in this very young age group. The need for a suitable formulation of praziquantel (e.g. syrup) must be emphasised, which will help to readily administer praziquantel to this age group.

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5. Efficacy and safety of two closely spaced doses of praziquantel against *Schistosoma haematobium* and *S. mansoni* and re-infection patterns in school-aged children in Niger

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5.1. Abstract

The aim of this study was to assess the efficacy and safety of two closely spaced doses of praziquantel (PZQ) against *Schistosoma haematobium* and *S. mansoni* infection in school-aged children, and to characterise re-infection patterns over a 12-month period. The study was carried out in five villages in western Niger: Falmado, Seberi and Libore (single *S. haematobium* infection foci), and Diambala and Namarigoungou (mixed *S. haematobium*-*S. mansoni* infection foci). Parasitological examinations consisted of triplicate urine filtrations and triplicate Kato-Katz thick smears at each visit. Two 40 mg/kg oral doses of PZQ were administered 3 weeks apart. Adverse events were monitored within 4 hours after dosing by the survey team and 24 hours after treatment using a questionnaire. Our final study cohort comprised 877 children who were infected with either *S. haematobium*, or *S. mansoni*, or both species concurrently and received both doses of PZQ. Follow-up visits were conducted 6 weeks, 6 months and 12 months after the first dose of PZQ. At baseline, the geometric mean (GM) infection intensity of *S. haematobium* ranged from 3.6 (Diambala) to 30.3 eggs/10 ml of urine (Falmado). The GM infection intensity of *S. mansoni* ranged from 86.7 (Diambala) to 151.4 eggs/gram of stool (Namarigoungou). Adverse events were reported by 33% and 1.5% of the children after the first and second dose of PZQ, respectively. We found cure rates (CRs) in *S. haematobium*-infected children 3 weeks after the second dose of PZQ ranging between 49.2% (Falmado) and 98.4% (Namarigoungou) and moderate to high egg reduction rates (ERRs) (71.4-100%). Regarding *S. mansoni*, only moderate CRs and ERRs were found (51.7-58.8% in Diambala, 55.2-60.2% in Namarigoungou). Twelve months post-treatment, prevalence rates approached pre-treatment levels, but infection intensities remained low. In conclusion, PZQ, given in two closely spaced doses, is efficacious against *S. haematobium*, but the low ERR observed against *S. mansoni* raises concern about mounting PZQ tolerance.

Keywords: Schistosomiasis, *Schistosoma haematobium*, *Schistosoma mansoni*, praziquantel, efficacy, safety, mixed infection, re-infection pattern, school-aged children, Niger

5.2. Introduction

Schistosomiasis, which is classified among the neglected tropical diseases (NTDs) (Hotez et al., 2006b; Molyneux et al., 2005; Utzinger et al., 2009), constitutes a considerable public health problem, particularly in Africa, where more than 95% of the cases are currently concentrated (Steinmann et al., 2006; Utzinger et al., 2009; Gryseels 2012). Ongoing efforts to re-evaluate the global burden due to schistosomiasis, taking into account also subtle morbidities, suggest that the burden could be as high as that owing to malaria (Hotez and Kamath, 2009; King and Dangerfield-Cha, 2008; Steinmann et al., 2006). In areas where schistosomiasis is highly endemic, the declared objective is to control morbidity (Savioli et al., 2009; WHO, 2002). Praziquantel (PZQ) is the drug of choice due to its good safety and therapeutic profile and ease of administration (single oral dose). Indeed, timely administration of PZQ improves the health and wellbeing of schistosome-infected people, and might prevent a significant proportion of HIV transmission in areas where HIV/AIDS and schistosomiasis co-exist (Hotez et al., 2009; Secor, 2012).

In 2001, the World Health Assembly (WHA) put forth resolution 54.19, which called upon member states to regularly treat at least 75% and up to 100% of all school-aged children at risk of schistosomiasis (WHO, 2002). Treatment should be extended to other high-risk groups (e.g. fishermen or entire communities) whenever appropriate. With regard to the control of schistosomiasis and other helminthiases, since 2006, the World Health Organization (WHO) promotes a strategy phrased “preventive chemotherapy”, which relies on the regular administration of anthelminthic drugs to at-risk populations without prior diagnosis (WHO, 2006, 2010). In the meantime, several national integrated NTD control programmes have been launched in Africa (Kolaczinski et al., 2007; Kabatereine et al., 2010; Dembélé et al., 2012). These programmes are supported by international organisations such as the Bill & Melinda Gates Foundation, the United States Agency of International Development (USAID), among others. The supply of PZQ is a crucial part of this strategy (Savioli et al., 2009; WHO, 2012). For the year 2010, for example, it has been reported that 33.5 million people were treated with PZQ, most of them (27.9 million) in Africa (WHO, 2012). However to reach the goal of WHA resolution 54.19, more than 100 million school-aged children in Africa alone require preventive chemotherapy with PZQ every year (Utzinger et al., 2009; Hotez et al., 2010; WHO, 2012). It is therefore anticipated that the use of PZQ will further increase in the years to come (Utzinger et al., 2009; Hotez and Pecoul, 2010; Hotez et al.,

2010). Mounting drug pressure might increase the likelihood of resistance development, and hence, there is a pressing need to monitor the efficacy of PZQ (WHO, 1998; Doenhoff et al., 2008) and to search for additional or alternative treatment strategies to prolong the useful life-span of PZQ (Doenhoff et al., 2009; Inyang-Etoh et al., 2009; Obonyo et al.). The use of multiple dose regimens is among these strategies (Picquet et al., 1998; Utzinger et al., 2000; Tchuem Tchuenté et al., 2001; N'Goran et al., 2003; Sacko et al., 2009). Two doses of PZQ, spaced by a few weeks, are of particular relevance in high transmission areas, where people might be infected with both juvenile and adult schistosome worms. Since the activity of PZQ is restricted to the adult schistosomes, a first dose of the drug will not clear the juvenile worms, but a few weeks later, these parasites have developed into adult worms that are then susceptible to a second dose of PZQ (Sabah et al., 1986, Utzinger et al., 2003, Doenhoff et al., 2008). Indeed, a recent systematic review quantified the incremental benefit of a second dose of PZQ, administered 2 to 8 weeks after an initial dose, for both *S. haematobium* and *S. mansoni* in Africa (King et al., 2011).

Adverse events due to PZQ are important issues as they can jeopardize compliance rate (Sissoko et al., 2009; Keiser et al., 2010; Obonyo et al., 2010). Indeed, high frequency of adverse events after PZQ administration are often reported (Berhe et al., 1999; Keiser et al., 2010; Lovis et al., 2012). These adverse events could be a cause of refusal of subsequent treatment rounds, and hence an important impediment for preventive chemotherapy programmes (Fleming et al., 2009). In-depth ethnographic research conducted in Uganda revealed that, among a host of other local dynamics, people may actively resist PZQ administration because of the tipping balance between adverse events and perceived benefits of deworming without prior diagnosis (Parker et al., 2008; Parker and Allen, 2011).

The objectives of this study were to assess the efficacy and safety of two closely spaced doses of PZQ against *S. haematobium* and *S. mansoni* infections among school-aged children and to investigate re-infection patterns. The study was carried out in five highly endemic villages of Niger, two of which are characterized by the co-existence of both schistosome species, and we used standard protocols and quality-controlled diagnostic methods.

5.3. Materials and methods

5.3.1. Study area

The study was carried out in five villages in the western part of Niger in the regions of Dosso and Tillaberi between March 2007 and June 2008 (Fig. 5.1). Falmado (geographical coordinates: 12.5138° N latitude, 2.8611° W longitude) is located in the district of Boboye in close proximity to a permanent pond in the valley of Dallol Bosso, which is a fossil river running only during the rainy season. According to a census done in 2007 (before launching the current study), there were 677 inhabitants. The main activity of the population is farming (e.g. cultivation of cassava, potato and vegetables). Only *S. haematobium* is transmitted in the village, with *Bulinus truncatus* serving as the main intermediate host snail. Although malacological surveys recorded the presence of *Biomphalaria pffeiferi*, an important intermediate host snail of *S. mansoni*, no such infections were observed among the populations (unpublished data).

Seberi (13.2944° N, 2.8611° W) and Libore (13.4027° N, 2.1902° W) are located in the district of Kollo, adjacent to irrigated fields of the Niger River valley. A population census carried out in 2001 reported total numbers of inhabitants of 1,635 and 2,464, respectively (National Census of the Population 2001). The main agricultural activity is rice farming with two harvests per year facilitated by an irrigation network established in the 1970s. Malacological surveys conducted in the area showed that only intermediate host snails of *S. haematobium* were present (Labbo et al., 2008).

Diambala (14.3149° N, 1.3009° W) and Namarigoungou (14.3667° N, 1.2571° W) are situated upstream of Tillaberi along the Niger River. The population sizes in Diambala and Namarigoungou are 5,116 and 3,256, respectively. These two villages are located in an irrigated rice farming perimeter. Both *S. haematobium* and *S. mansoni* are transmitted in this area, with *S. mansoni* only quite recently (Labbo et al., 2003; Garba et al., 2004).

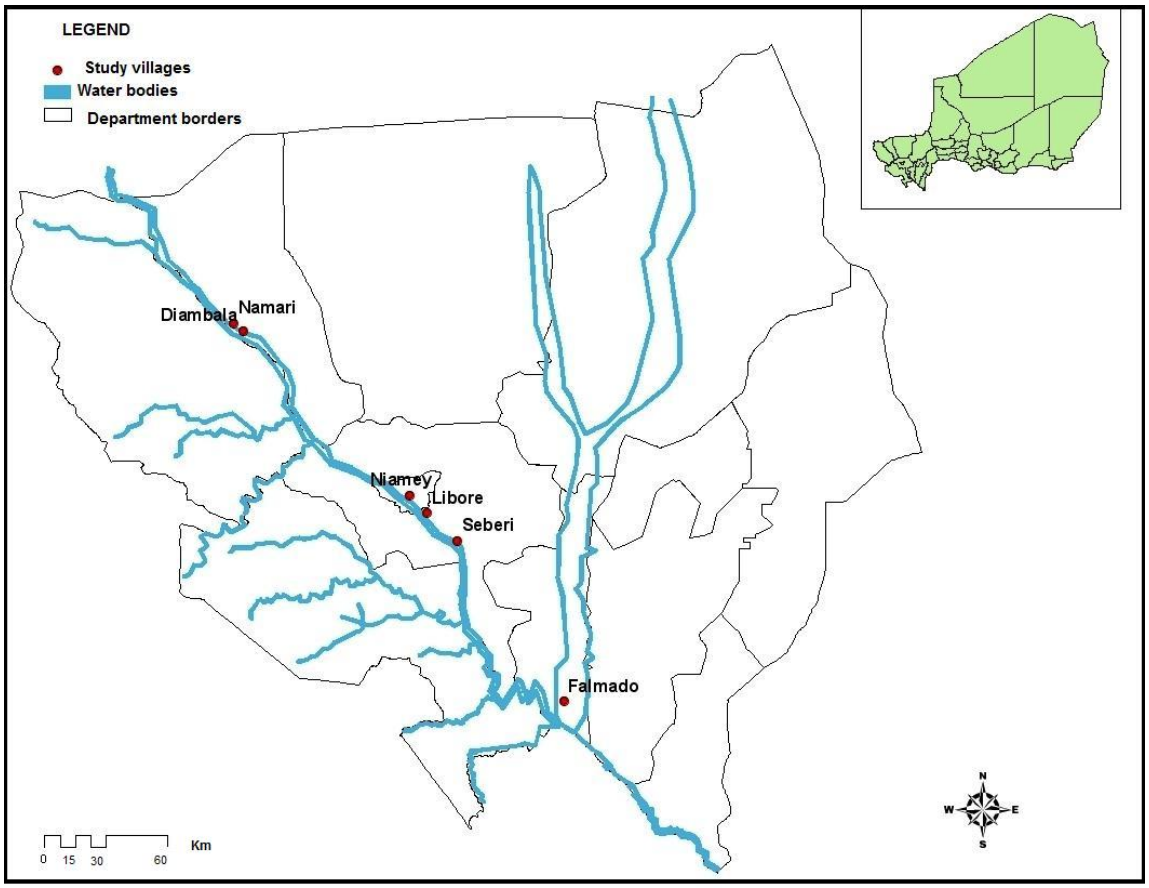

Fig. 5.1. Map showing the location of the five study villages in Niger where the efficacy and safety of two closely spaced doses of praziquantel treatments, including re-infection patterns were studied in 2007 and 2008.

5.3.2. Study design

The epidemiological design of the study presented here was a 12-month longitudinal cohort study after a treatment intervention. Children were orally administered PZQ at the dose of 40 mg/kg at baseline and 3 weeks later. Follow-up surveys were carried out 6 weeks, 6 months and 12 months after the first dose of PZQ. Inclusion criteria were (i) acceptance to participate in the study; (ii) children aged 6-15 years; (iii) infection with either *S. haematobium*, or *S. mansoni*, or both species concurrently during baseline; and (iv) residency in the study villages for at least one year.

5.3.3. Ethics statement and operational considerations

The study received approval from the national ethics committee of Niger (reference no. N01/2008/CCNE). The regional and district health and education authorities and the traditional and religious chiefs of the surveyed villages were informed of the study and kindly

asked to provide logistical support to our research team. The objectives and procedures of the study were explained to the parents or legal guardians of participating children. Due to the high illiteracy rate in these communities, we opted for oral rather than written informed consent. One month after the second dose of PZQ, preventive chemotherapy was provided by the national schistosomiasis and soil-transmitted helminthiasis control programme, and the five villages described here, were all included. At-risk populations were offered free PZQ (single 40 mg/kg oral dose) and albendazole (single 400 mg oral dose). Great care was taken not to re-treat children of our cohort.

5.3.4. Field and laboratory procedures

Each child included in the study was invited to provide three urine samples (collected over three consecutive days) per survey, the baseline cross-sectional and each of the three follow-up surveys. Urine samples were collected between 10:30 and 14:00 hours and standard protocols were followed for diagnosis (WHO, 1985). In brief, urine samples were vigorously shaken and 10 ml were filtered using 13 mm diameter nucleopore filters. The filters were placed on a microscope slide, a drop of Lugol's iodine was added, and then examined under a microscope by experienced laboratory technicians. The number of *S. haematobium* eggs per slide were counted and recorded for each child separately. Additionally, from children in Diambala and Namarigoungou, three stool samples were collected per survey over three consecutive days. The samples were subjected to the Kato-Katz technique with single 41.7 mg thick smears prepared from each sample (Katz et al., 1972).

The laboratory examinations took place on site in Falmado, Diambala and Namarigoungou. For Libore and Seberi, which are located 25-40 km from Niamey, the samples were transferred and examined in our laboratory the same day.

We classified intensity of schistosome infections according to WHO guidelines (WHO, 2002). In brief, for *S. haematobium*, we stratified into light (1-49 eggs/10 ml of urine) and heavy infections (≥50 eggs/10 ml of urine). The intensity of *S. mansoni* infection was classified into light (1-99 eggs per gram of stool (EPG)), moderate (100-399 EPG) and heavy infections (≥400 EPG). We adhered to the following system of quality control: each day, 10 slides from each technician were re-examined by a senior technician to check for internal consistency (acceptance rate: <10% of error rates).

5.3.5. Treatment and monitoring of adverse events

After the baseline survey, all children were given PZQ (MED-PHARMN; batch Nb. 06L11B) at a dose of 40 mg/kg. Children's weight was measured with a digital scale. Treatment was administered early in the morning at school before children entered their class rooms, hence shortly after they had taken their breakfast at home. Treatment was accompanied by an orange juice, provided free of charge by the research team. Children were re-treated 3 weeks later with the same dose and batch of PZQ.

For a period of 4 hours, children remained under medical supervision. In case vomiting occurred within 1 hour, children were re-dosed. Acute adverse events were recorded and appropriate measures taken by the study physician of our team. Twenty-four hours post-treatment, children were invited to fill-in a questionnaire about any adverse events that occurred since drug administration.

5.3.6. Statistical analysis

Data were entered into an Excel spreadsheet and analysed with EpiInfo 2000. Only those children who were found positive for *S. haematobium* and/or *S. mansoni* at the baseline cross-sectional survey and had taken PZQ twice were considered for analysis (per-protocol analysis).

PZQ efficacy was assessed by determining both the cure rate (CR) and the egg reduction rate (ERR). The CR is defined as the proportion of individuals infected either with *S. haematobium* or *S. mansoni* at baseline who became egg-negative 6 weeks after the first dosing. The CR 6 months after the first dose of PZQ was also determined. ERR was defined as the percentage reduction of the geometric mean (GM) egg counts for the positive individuals. The GM was calculated as the antilogarithm of the mean of the log-transformed egg counts only for the positive individuals. Our data also allowed characterising re-infection patterns, i.e. the proportion of children who were egg-negative 6 weeks after the first dosing but became egg-positive 6 and 12 months post-treatment.

P-values <0.05 were considered to indicate statistical significance. We compared proportions using the Pearson χ^2 with Yates correction as appropriate. GM egg counts among different groups were compared using ANOVA.

5.4. Results

5.4.1. Study profile and compliance

Fig. 5.2 shows the study profile, including the numbers of children participating at the various follow-up time points, stratified by village. Overall, 1,558 children of school-age were enrolled in the baseline cross-sectional survey. These children provide urine samples alone or both urine and stool samples in the mixed *S. haematobium-S. mansoni* transmission foci. The baseline parasitological screening revealed the highest prevalence of *S. haematobium* in Falmado (99.0%) followed by Libore (93.9%). A considerably lower prevalence was found in Namarigoungou (46.5%).

The overall prevalence of *S. mansoni* was 66.2% in Namarigoungou and 62.4% in Diambala. The prevalence of mixed *S. haematobium-S. mansoni* infection was 41.6% in Diambala and 35.3% in Namarigoungou. According to the baseline survey, the total number of children with a *Schistosoma* infection was 1,205 (77.4% of the initially screened children). A total of 877 children received both doses of PZQ and were followed-up at 6 weeks, 6 months and 12 months post-treatment.

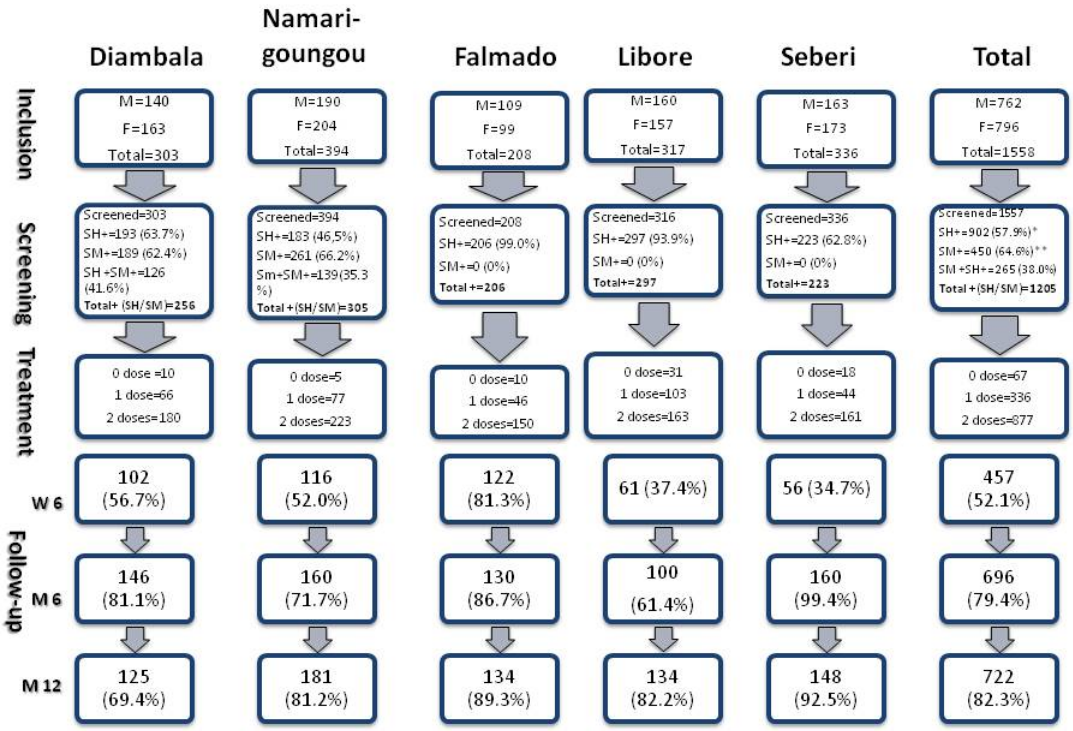

Fig. 5.2. Survey profile chart comprising the number of children included, *Schistosoma haematobium* (Sh) and *S. mansoni* (Sm) prevalences at the baseline cross-sectional survey, the treatment rate and the attendance rate 6 weeks (W6), 6 months (M6) and 12 months (M12) after the first dose of two closely spaced doses of praziquantel.

The characteristics of the children (number, sex and age) who were retained for the final analysis are summarised in Table 5.1. Stratified by village, between 150 (Falmado) and 223 (Namarigoungou) children participated. There were more girls than boys with a sex ratio female:male of 1.2. The average age was 9.3 years with a range of 6 to 16 years. The youngest average age was noted in Falmado (8.2 years), while in Diambala the average age was 9.9 years.

The compliance rates at the various follow-up surveys varied and we observed considerable differences from one village to another (Fig. 5.2). A particularly low compliance rate occurred 6 weeks after the first dose of PZQ (52.1%), which coincided with the long school holidays. Compliance at the 6 and 12 months post-treatment follow-ups were 79.4% and 82.3%, respectively.

Table 5.1. Characteristics of the surveyed school-aged children in five study villages in Niger in early 2007.

Characteristics	Single *S. haematobium* transmission foci				Mixed *S. haematobium*-*S. mansoni* transmission foci			Overall total
	Libore	Seberi	Falmado	Total	Namarigoungou	Diambala	Total	
No. of children examined	163	161	150	474	223	180	403	877
No. (%) of girls	77 (47.2)	87 (54.0)	90 (60.0)	254 (53.6)	128 (57.4)	99 (55.0)	227 (56.3)	481 (54.8)
No. (%) of boys	86 (52.8)	74 (46.0)	60 (40.0)	220 (46.4)	95 (42.6)	81 (45.0)	176 (43.7)	396 (45.2)
Mean age (SD) in years	9.0 (1.8)	9.0 (1.9)	8.2 (2.9)	9.1 (2.2)	9.3 (1.9)	9.9 (2.0)	9.6 (1.9)	9.3 (2.1)

SD, standard deviation

Table 5.2. Number (%) of acute adverse events (AEs) within 4 hours and solicited AEs (within 4-24 hours) reported by school-aged children (n=874) after the first and second dose of praziquantel (PZQ), spaced by 3 weeks, in a study carried out in five villages in Niger in 2007

Adverse event	No. (%) of AEs after the first dose of PZQ		No. (%) of AEs after the second dose of PZQ	
	Acute AEs	Solicited AEs	Acute AEs	Solicited AEs
Abdominal pain	119 (13.6)	29 (3.3)	4 (0.5)	0
Sleepiness	38 (4.4)	0	0	0
Headache	32 (3.7)	2 (0.2)	2 (0.2)	0
Itching	26 (3.0)	0	0	0
Vomiting	26 (3.0)	6 (0.7)	6 (0.7)	0
Skin rash	18 (2.1)	12 (1.4)	0	0
Nausea	15 (1.7)	1 (0.1)	0	0
Asthma	7 (0.8)	3 (0.3)	0	0
Dizziness	5 (0.6)	0	0	0
Haematuria	2 (0.2)	0	0	0
Fever	0	1 (0.1)	1 (0.1)	0
Total	288 (33.0)	54 (6.2)	13 1.5)	0

5.4.2. Safety of PZQ

Acute (within 4 hours) and solicited (within 4-24 hours) adverse events after the first and second dose of PZQ are shown in Table 5.2. As expected, the frequency of adverse events was higher after administration of the first dose of PZQ than the second one. Most of the adverse events occurred within 4 hours after PZQ administration; there were 288 acute adverse events *versus* 54 solicited adverse events after the first dose of PZQ. The respective numbers after the second dose dropped to 13 and nil. Abdominal pain was the most common adverse event (13.6% after the first dose of PZQ), followed by sleepiness (4.4%) and headache (3.7%).

5.4.2.1. Efficacy of PZQ against S. haematobium

The efficacy of PZQ against *S. haematobium* infection determined 6 weeks and 6 months after the first dose of PZQ are shown in Table 5.3. In the single *S. haematobium* transmission foci, the GM egg counts at baseline varied from 4.9 (Seberi) to 30.3 eggs/10 ml of urine (Falmado). The prevalence of heavy infections (≥50 eggs/10 ml of urine) in these two villages was 5.6% and 38.8%, respectively. In Diambala and Namarigoungou, the two villages where *S. mansoni* co-exists, the GM of *S. haematobium* was 3.6 and 4.0 eggs/10 ml of urine, respectively.

At the first follow-up time point, i.e. 6 weeks after the first and 3 weeks after the second dose of PZQ, CRs in Namarigoungou and Diambala were 98.4% and 96.0%, respectively. In the single *S. haematobium* transmission foci, the CRs were considerably lower, varying between 49.2% (Falmado) and 58.9% (Seberi). Among children who were still infected after these two closely spaced PZQ doses, infections were all of low intensity (<50 eggs/10 ml of urine). ERRs in the single *S. mansoni* transmission foci varied between 71.4% (Seberi) and 92.1% (Falmado).

Six months post-treatment, the observed CRs were higher in Namarigoungou and Diambala (both 100%) than in Seberi (82.5%), Falmado (57.7%) and Libore (42.0%). The GM egg counts had decreased to 2.8 eggs/10 ml of urine in Falmado. However, two of the treated children (1.5%) still presented with a heavy infection.

Table 5.3: Efficacy of two closely spaced doses of praziquantel (PZQ) against *S. haematobium* in five villages of Niger determined 6 weeks and 6 months after the first dose of PZQ and re-infection rates at 6 and 12 months post-treatment.

	Single *S. haematobium* transmission foci					**Mixed *S. haematobium*-*S. mansoni* transmission foci**			
	Libore	**Seberi**	**Falmado**	**Total**	***P*-value**	**Namarigoungou**	**Diambala**	**Total**	***P*-value**
Before treatment									
No. of infected children treated with PZQ	163	161	150	474		133	136	269	
No. (%) of children ≥50 eggs/10 ml of urine	50 (30.7)	9 (5.6)	57 (38.8)	116 (24.5)	<0.001	0 (0.0)	1 (0.7)	1 (0.4)	n.a.
GM egg count per 10 ml of urine (SD)	18.8 (5.3)	4.9 (3.8)	30.3 (3.5)	13.9 (5.1)	<0.001	4.0 (2.3)	3.6 (2.4)	3.7 (2.3)	0.055
6 weeks post-treatment									
No. of children examined	61	56	122	239		63	75	138	
No of children cured (CR in %)	34 (55.7)	33 (58.9)	60 (49.2)	127 (53.1)	0.430	62 (98.4)	72 (96.0)	134 (97.1)	0.740
No. of children ≥50 eggs/10 ml of urine	0	0	0	0		0	0	0	
GM egg count/10 ml of urine (SD)	2.1 (2.5)	1.4 (1.7)	2.4 (1.5)	2.1 (2.5)	0.001	-	-	-	
ERR in %	88.2	71.4	92.1	84.9	<0.001	100.0	100.0	100.0	n.a.
6 months post-treatment									
No. of children examined	100	160	130	390		95	110	205	
No of children cured (CR in %)	42 (42.0)	132 (82.5)	75 (57.7)	248 (63.6)	<0.001	95 (100.0)	110 (100.0)	205 (100.0)	n.a.
No. (%) of children ≥50 eggs/10 ml of urine	0	0	2 (1.5)	2 (0.5)		-	-	-	
GM egg count/10 ml of urine (SD)	2.5 (2.8)	1.4 (1.7)	2.8 (3.0)	2.3 (2.8)	<0.001	-	-	-	
ERR in %	86.7	71.4	90.8	83.5	<0.001	100.0	100.0	100.0	n.a.
No. of children reinfected/surveyed (%)	17/24 (70.8)	2/33 (6.1)	25/54 (46.3)	44/111 (39.6)	<0.001	0.0	0.0	0.0	n.a.
12 months post-treatment									
No. of children examined	134	148	134	416		107	88	195	
No. (%) of children positive	125 (93.3)	79 (53.4)	83 (61.9)	287 (69.0)	<0.001	0 (0.0)	5 (5.7)	5 (2.6)	0.041
No. (%) of children ≥50 eggs/10 ml of urine	15 (11.2)	1 (0.7)	2 (1.5)	18 (4.3)	<0.001	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
GM egg count/10 ml of urine (SD)	6.0 (4.8)	2.1 (2.6)	1.9 (2.9)	3.2 (4.1)	<0.001	-	1.9 (1.7)	1.5 (1.7)	n.a.
ERR (in %)	68.1	57.1	93.7	76.9	<0.001	100.0			
No. of children reinfected/surveyed (%)	27/28 (96.4)	12/28 (42.9)	27/53 (50.9)	66/109 (60.6)	<0.001	0/53 (0.0)	4/49 (8.2)	4/102 (3.9)	0.107

CR, cure rate; ERR, egg reduction rate; GM, geometric mean; n.a., not assessed; SD, standard deviation.

5.4.2.2. Efficacy of PZQ against S. mansoni

The efficacy of two closely spaced doses of PZQ against *S. mansoni* infection in the two villages where both *S. haematobium* and *S. mansoni* co-exist are summarised in Table 5.4. At baseline, the level of *S. mansoni* infection was significantly higher in Namarigoungou than in Diambala (GM faecal egg counts: 151.4 EPG *vs.* 86.7 EPG, P <0.001). The prevalence of light infections (1-99 EPG) was 49.3% in Diambala and 27.5% in Namarigoungou.

Two closely spaced doses of PZQ yielded similar CRs against *S. mansoni*: 60.2% in Namarigoungou and 58.8% in Diambala, as determined at the 6-week follow-up. The ERRs in the two villages were also comparable: 55.2% and 51.7%, respectively. Six months post-treatment, the apparent CR in Diambala remained at the same level (59.0%), while it had dropped to 24.2% in Namarigoungou. However, no heavy *S. mansoni* infections (≥400 EPG) were observed in either village. The 6-month ERRs among infected children were 70.3% in Namarigoungou and 69.7% in Diambala.

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Table 5.4: Efficacy of two closely spaced praziquantel (PZQ) doses administered to school-aged children infected with *S. mansoni* in two villages of Niger determined 6 weeks and 6 months after the first dose of PZQ and re-infection levels at 6 and 12 months post-treatment follow-up surveys.

	Diambala	**Namarigoungou**	**Total**	***P*-value**
Before treatment				
No. of infected children treated with PZQ	140	193	333	
No. (%) of children with light infection (1-99 EPG)	69 (49.3)	53 (27.5)	122 (36.6)	<0.001
No. (%) of children with moderate infection (100-399 EPG)	61 (43.6)	116 (60.1)	177 (53.2)	0.003
No. (%) of children with heavy infection (≥400 EPG)	10 (7.1)	24 (12.4)	34 (10.2)	0.115
GM egg count/g of stool (SD)	86.7 (2.4)	151.4 (2.7)	124.9 (2.7)	<0.001
6 weeks post-treatment				
No. of children examined	80	103	183	
No of children cured (CR in %)	47 (58.8)	62 (60.2)	109 (59.6)	0.843
No. (%) of children with light infection (1-99 EPG)	30 (37.5)	29 (28.2)	59 (32.2)	0.180
No. (%) of children with moderate infection (100-399 EPG)	3 (3.8)	11 (10.7)	14 (7.7)	0.080
No. (%) of children with heavy infection (≥400 EPG)	0 (0.0)	1 (1.0)	1 (0.5)	n.a.
GM egg count/g of stool (SD)	41.9 (2.3)	67.9 (2.5)	54.8 (2.5)	<0.001
ERR in %	51.7	55.2	56.1	0.582
6 months post-treatment				
No. of children examined	117	149	266	
No of children cured (CR in %)	69 (59.0)	36 (24.2)	105 (39.5)	<0.001
No. (%) of children with light infection (1-99 EPG)	43 (36.8)	88 (59.1)	131 (49.2)	<0.001
No. (%) of children with moderate infection (100-399 EPG)	5 (4.3)	25 (16.8)	30 (11.3)	0.001
No. (%) of children with heavy infection (≥400 EPG)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
GM egg count/g of stool (SD)	26.3 (2.6)	44.9 (2.9)	38.3 (2.9)	<0.001
ERR in %	69.7	70.3	69.3	0.946
No. of children reinfected/surveyed (%)	16/42 (38.1)	40/54 (74.1)	56/96 (63.4)	<0.001
12 months post-treatment				
No. of children examined	104	158	262	
No. (%) of children with no infection	48 (46.2)	42 (26.6)	90 (34.4)	0.001
1-99 EPG (%)	48 (46.2)	96 (60.8)	144 (55.0)	0.020
100-399 EPG (%)	7 (6.7)	19 (12.0)	26 (9.9)	0.161
≥400 EPG (%)	1 (1.0)	1 (0.6)	2 (0.8)	n.a.
GM egg count/g of stool (SD)	43.6 (2.8)	46.1 (2.6)	45.3 (2.6)	<0.001
ERR in %	49.7	69.6	63.7	0.001
No. of children reinfected/surveyed (%)	24/39 (61.5)	35/54 (64.8)	59/93 (63.4)	0.746

CR, cure rate; EPG, eggs per gram of stool; ERR, egg reduction rate; GM, geometric mean; n.a., not assessed; SD, standard deviation.

5.4.2.3. Efficacy of PZQ in mixed versus single S. haematobium *and* S. mansoni *infections*

The data presented here were only from the two villages (Namarigoungou and Diambala) with *S. haematobium* and *S. mansoni* co-exist. Table 5.5 shows the efficacy of two closely spaced PZQ doses against *S. haematobium* in the two villages were *S. haematobium* and *S. mansoni* are co-endemic. At baseline, the GM infection intensity of *S. haematobium* was higher in children concurrently infected with *S mansoni* than a *S. haematobium* mono-infection (3.9 *vs.* 3.2; P =0.032). At the 6-week treatment follow-up, the GM infection intensity of *S. haematobium* was still higher in those children concurrently infected with *S. mansoni* than the *S. haematobium* mono-infected ones (2.1 *vs.* 1.0, P <0.001), owing to a significantly different ERR. At the 6-month treatment follow-up, all investigated children were apparently cured, and hence no differences observed regardless of whether children had a mono- or co-infection at baseline.

With regard to efficacy of two closely spaced doses of PZQ against *S. mansoni* in the mixed transmission villages, at baseline, the prevalence of heavy *S. mansoni* infections (≥400 EPG) was 12.1% in the co-infected subjects and 7.5% in those presenting a single *S. mansoni* infection, with no statistically significant difference between the two groups (Table 6). The GM faecal egg count was significantly higher in the co-infected children compared to the single *S. mansoni*-infected children (2.8 *vs.* 2.5, P <0.001). Six weeks post-treatment, the CR was similar between the two groups: 56.7% in co-infected children and 63.3% in those infected with *S. mansoni* singly (P = 0.370). ERRs were also comparable: 53.4% in co-infected and 60.0% in the single-infected subjects (Table 5.6). Six months after the administration of two doses of PZQ, the CR was 40.0% in the co-infected subjects and 38.6% in the single-infected children. No heavy infections were observed in either group. Similar ERRs were observed: 69.3% in the mixed infections and 69.4% in the group singly infected with *S. mansoni*.

Table 5.5: Efficacy of two closely spaced doses of praziquantel (PZQ) against *S. haematobium* in two villages of Niger where both *S. haematobium* and *S. mansoni* co-exist (Namarigoungou and Diambala), as determined 6 weeks and 6 months after the first dose of PZQ. Data are stratified by children with single *S. haematobium* or mixed *S. haematobium*-*S. mansoni* infection. Re-infection patterns at 6 and 12 months post-treatment are also shown

Characteristics	**Total**	***S. haematobium* mono-infection**	***S. haematobium*-*S. mansoni* mixed infection**	***P*-value**
Before treatment				
No. of *S. haematobium*-infected children	269	70	199	
No. (%) of children ≥50 eggs/10 ml of urine	1 (0.4)	0 (0.0)	1 (0.5)	n.a.
GM egg count/10 ml of urine (SD)	3.7 (2.3)	3.2 (2.2)	3.9 (2.4)	0.032
6 weeks post-treatment				
No. of children examined	138	34	104	
No of children cured (CR in %)	134 (97.1)	32 (94.1)	102 (98.1)	0.223
No. (%) of children ≥50 eggs/10 ml of urine	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
GM egg count/10 ml of urine (SD)	2.1 (1)	1.0 (1)	2.1 (1)	<0.001
ERR in %	43.2	68.8	46.2	0.029
6 months post treatment				
No. of children examined	205	39	166	
No of children cured (CR in %)	205 (100.0)	39 (100.0)	166 (100.0)	n.a.
No. (%) of children ≥50 eggs/10 ml of urine	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
GM egg count/10 ml of urine (SD)	0.0	-	-	
ERR in %	100.0	100.0	100.0	n.a.
No. of children re-infected/surveyed (%)	0/269 (0.0)	0/39 (0.0)	0/166 (0.0)	n.a
12 months post treatment				
No. of children examined	195	42	153	
No. (%) of children ≥50 eggs/10 ml of urine	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
GM egg count/10 ml of urine (SD)	1.9 (2.1)	2.0 (1.0)	1.9 (2.3)	0.687
ERR in %	48.6	37.5	51.3	0.139
No. of children re-infected/surveyed (%)	4/99 (4.0)	1/19 (5.3)	3/80 (3.8)	

CR, cure rate; ERR, egg reduction rate; GM, geometric mean; n.a., not assessed; SD, standard deviation.

Table 5.6: Efficacy of two closely spaced doses of praziquantel (PZQ) against *S. mansoni* in two villages of Niger where both *S. mansoni* and *S. haematobium* co-exist (Namarigoungou and Diambala), as determined 6 weeks and 6 months after the first dose of PZQ. Data are stratified by children with single *S. mansoni* or mixed *S. mansoni*-*S. haematobium* infection. Re-infection patterns at 6 and 12 months post-treatment are also shown.

Characteristics	Overall *S. mansoni*	*S. mansoni* mono-infection	*S. mansoni*-*S. haematobium* mixed infection	*P*-value
Before treatment				
No. of *S. mansoni*-infected children	333	134	199	
No. (%) of children with light infection (1-99 EPG)	122 (36.6)	50 (37.3)	72 (36.2)	0.833
No. (%) of children with moderate infection (100-399 EPG)	177 (53.2)	74 (55.2)	103 (51.8)	0.534
No. (%) of children with heavy infection (≥400 EPG)	34 (10.2)	10 (7.5)	24 (12.1)	0.174
GM egg count/g of stool (SD)	124.9 (2.7)	123.4 (2.5)	125.9 (2.8)	<0.001
6 weeks post-treatment				
No. of children examined	185	79	104	
No of children cured (CR in %)	109 (59.6)	50 (63.3)	59 (56.7)	0.370
No. (%) of children with light infection (1-99 EPG)	59 (32.2)	26 (32.9)	33 (31.7)	0.866
No. (%) of children with moderate infection (100-399 EPG)	14 (7.7)	2 (2.5)	12 (11.5)	0.023
No. (%) of children with heavy infection (≥400 EPG)	1 (0.0)	1 (1.3)	0 (0.0)	
GM egg count/g of stool (SD)	54.8 (2.5)	49.3 (2.4)	58.7 (2.5)	<0.001
ERR in %	56.1	60.0	53.4	0.446
6 months post treatment				
No. of children examined	266	101	165	
No of children cured (CR in %)	105 (39.5)	39 (38.6)	66 (40.0)	0.822
No. (%) of children with light infection (1-99 EPG)	131 (49.2)	50 (45.5)	81 (49.1)	0.574
No. (%) of children with moderate infection (100-399 EPG)	30 (11.3)	12 (11.9)	18 (10.9)	0.808
No. (%) of children with heavy infection (≥400 EPG)	0 (0.0)	0 (0.0)	0 (0.0)	
GM egg count/g of stool (SD)	38.3 (2.9)	37.7 (3.1)	38.7 (2.8)	<0.001
ERR in %	69.3	69.4	69.3	0.970
No. of children re-infected/surveyed (%)	56/96 (63.4)	25/28 (89.3)	31/58 (60.8)	0.006
12 months post treatment				
No. of children examined	262	109	153	
No of children cured (CR in %)	90 (34.4)	39 (35.8)	51 (33.3)	0.681
No. (%) of children with light infection (1-99 EPG)	144 (55.0)	57 (52.3)	87 (56.9)	0.464
No. (%) of children with moderate infection (100-399 EPG)	26 (9.9)	12 (11.0)	14 (9.2)	0.620
No. (%) of children with heavy infection (≥400 EPG)	2 (0.8)	1 (0.9)	1 (0.7)	
GM egg count/g of stool (SD)	45.3 (2.6)	48.7 (2.6)	43.1 (2.6)	<0.001
ERR in %	63.7	60.5	65.8	0.365
No. of children re-infected/surveyed (%)	59/93 (63.4)	30/42 (71.4)	29/51 (56.9)	0.147

CR, cure rate; EPG, eggs per gram of stool; ERR, egg reduction rate; GM, geometric mean; SD, standard deviation.

5.4.3 Re-infection patterns

Patterns of re-infection with *S. haematobium* in the single transmission foci showed strong idiosyncrasies from one village to another. While only 6.1% of the surveyed children Seberi were re-infected 6 months after two closely spaced PZQ doses, the respective prevalences in Falmado and Libore were 46.3% and 70.8% (Table 3). In the two villages where both *S. haematobium* and *S. mansoni* co-exist, no re-infection with *S. haematobium* was observed among 205 children who were present at the 6-month follow-up (76.2% of the children included). Twelve months post-treatment, 27 out of 28 children surveyed in Libore were re-infected with *S. haematobium* (96.4%). In Falmado, at this post-treatment follow-up, half of the children surveyed were re-infected (50.9%), and only a slightly lower prevalence was found in Seberi (42.9%). The prevalence of heavy infections (≥50 eggs/10 ml of urine) at the 12-month follow-up varied between 0.7% (Seberi; the village with the lowest baseline infection prevalence) and 11.2% (Libore; the village with the highest baseline infection prevalence).

In the *S. haematobium-S. mansoni* mixed transmission foci, the overall prevalence of *S. haematobium* was 2.6% among the 195 children (72.4% of the subjects included) who were re-examined 12 months post-treatment. No re-infection occurred in Namarigoungou and only four out of 49 children surveyed were re-infected in Diambala (8.2%). There were no heavy *S. haematobium* infections at the 12-month follow-up. The re-infection rate of those children who were negative 6 weeks after treatment was 8.2% in Diambala (Table 5.3).

With regard to *S. mansoni* re-infection patterns, 12 months after PZQ administration, we observed infection prevalences of 53.8% in Diambala and 73.4% in Namarigoungou and respective GM faecal egg counts of 43.6 EPG and 46.1 EPG (Table 5.4). Heavy infections (≥400 EPG) were found in two children (0.8%). Almost two third of the children surveyed were re-infected with *S. mansoni* at this 12-months post-treatment follow-up (61.5% in Diambala and 64.8% in Namarigoungou). As can be seen in Table 5.6, the prevalence of *S. mansoni* at the 12-month post-treatment follow-up was similar between children who were infected with *S. mansoni* only (64.2%) and those with a *S. mansoni-S. haematobium* co-infection at baseline (66.7%). Moreover, the GM *S. mansoni* faecal egg counts at the 12-month follow-up in the two groups were similar (48.7 EPG *vs.* 43.1 EPG). Approximately two third of the children were re-infected with *S. mansoni* at the 12-month post-treatment follow-

up (63.4%), with a slightly higher prevalence among those children who had a *S. mansoni* mono-infection at baseline (71.4%) compared with those who were co-infected at baseline (56.9%), but the difference showed no statistical significance ($P = 0.147$).

5.5. Discussion

Our study is among the few investigations assessing the efficacy and safety of two closely spaced doses of PZQ (40 mg/kg each, given 3 weeks apart) against schistosomiasis. Such a strategy has been proposed as a means of improving PZQ effectiveness (Tchuem Tchuenté et al., 2001; King et al., 2011). Indeed young developing stages of schistosomes (i.e. schistosomula) are largely refractory to PZQ. However, administering a second dose of PZQ several weeks later should kill these parasites as they have matured (Doenhoff et al., 2008). Our study was conducted in the western part of Niger, one of the most intense schistosomiasis transmission zones encountered in West Africa. While *S. haematobium* is the principal schistosome species, there are also mixed *S. haematobium*-*S. mansoni* foci affecting already preschool-aged children (Tchuem Tchuenté et al., 2004; Garba et al., 2010).

The overall compliance rate over the 12-month course of the study was acceptable with the exception of the 6-week post-treatment follow-up, which coincided with the long school holidays. Our final compliance rate 12 months after the first dose of PZQ (82.3%) was comparable to rates observed in Côte d'Ivoire, which ranged from 70% to 83% in four villages (N'Goran et al., 2001). In a study carried out in Cameroon, the 6-week post-treatment participation rate was 87%. However, due to changes in the school calendar, it dropped to 41% another 3 weeks later when schools were on vacation (Tchuem Tchuenté et al., 2004).

In terms of efficacy, we found moderate CRs 6 weeks post-treatment against *S. haematobium* in the single transmission foci (49.2-58.9%), and moderate-to-high ERRs (71.4-92.1%). Interestingly, considerably higher CRs were observed against *S. haematobium* in the mixed infection foci (96.0-98.4%) and ERRs approaching 100%. These observations point to the importance of monitoring PZQ efficacy in single and mixed *Schistosoma* transmission foci (Gouvras et al., 2012). Importantly though, the CRs observed in the single *S. haematobium* transmission foci are lower than the CR reported in a previous study (Garba et al., 2001), i.e. 68% 6 weeks after a single 40 mg/kg oral dose of PZQ, although the GM egg count at baseline was similar (35 eggs/10 ml of urine). Moreover, the ERR was higher in the

previous study using a single dose of PZQ (98.8% *vs.* 84.9% in the current study with a two-dose regimen). While these findings might point to mounting PZQ tolerance, care is indicated because of the low 6-week compliance rate in the present study (approximately 50%). Sacko and colleagues, in a study conducted in two villages in Mali, assessed the efficacy of two closely spaced doses of PZQ (40 mg/kg each, given 2 weeks apart). Three months post-treatment, CRs of 46.0% (Koulikoro) and 56.8% (Silengue) were obtained, hence similar to our findings in the Niger River valley (Sacko et al., 2009). CRs and ERRs are associated with pre-treatment infection intensity, as shown in previous studies (Olds et al., 1999; Utzinger et al., 2000; Gryseels et al., 2001; N'Goran et al., 2003). Tchuem Tchuenté and colleagues in Cameroon, adhering to the same treatment protocol as in the present study, obtained a higher CR (82.1%) and ERR (98.7%) (Tchuem Tchuenté et al., 2004). However, the baseline infection intensity was lower in the Cameroon study (19 eggs/10 ml of urine) compared to the present study (30 eggs/10 ml of urine in Falmado). N'Goran and colleagues also obtained higher CRs and ERRs among school-aged children in south-central Côte d'Ivoire (N'Goran et al., 2003) with similar pre-treatment infection intensity (23.8 eggs/10 ml of urine and 29.4% excreting ≥50 eggs/10 ml of urine). The post-treatment evaluation was done 3 weeks after the second dose of PZQ, but the interval between the two PZQ doses was 4 weeks while in the current study in Niger and the investigation done in Cameroon (Tchuem Tchuenté et al., 2004), it was 1 week shorter. The observed CR in the aforementioned Côte d'Ivoire study was 93% and the ERR was 96.6%. Midzi and colleagues in Zimbabwe administered two doses of 40 mg/kg PZQ with an interval of 6 weeks in a highly endemic area for *S. haematobium* (33.8% of the children excreting ≥50 eggs/10 ml of urine) (Midzi et al., 2008). Drug efficacy evaluation in our study was undertaken 3 weeks after the second dose and showed high CR (88.5%) and ERR (98.2%). We speculate that the time interval between two doses of PZQ should be somewhat longer than 3 weeks as investigated in Niger (current study) and Cameroon (Tchuem Tchuenté et al., 2004), as the research conducted in Côte d'Ivoire (interval: 4 weeks) (N'Goran et al., 2003) and Zimbabwe (interval: 6 weeks) (Midzi et al., 2008) showed higher efficacy. Moreover, we conjecture that the 3-week interval between the second dosing and drug efficacy evaluation might have been too short, as it might have still detected the tail of egg excretion (Danso-Appiah et al., 2009). This issue might explain the apparent improvement of the results at the 6-month post-treatment follow-up. To clarify this issue, we propose a study, where a cohort of individuals infected with *S. haematobium* is

followed-up weekly for at least 2 months after a single 40 mg/kg oral dose of PZQ, similar to a recent study done for *S. mansoni* (Scherrer et al., 2009).

With regard to *S. mansoni*, only moderate CRs (58.8-60.2%) and ERRs (51.7-55.2%) were observed after two closely spaced doses of PZQ. The overall GM faecal egg count of those children who remained infected was 54.8 EPG 3 weeks after the second dose of PZQ. The current study represents the first investigation to assess the efficacy of PZQ against *S. mansoni* in this emerging focus of Niger, where only *S. haematobium* was present 10 years ago (Garba et al., 2004). No apparent improvements were observed in terms of CR and ERR at the 6-month post-treatment follow-up. A similarly low CR (58.1%) and ERR (56.2%) was observed in Ndombo, Senegal, after two 40 mg/kg PZQ doses given 4 weeks apart (Tchuem Tchuenté et al., 2001). The GM faecal egg count in this Senegal study was approximately 3-fold higher than in our study. However, only 43 individuals were included in the Senegal study, and hence care is indicated when interpreting those results. In a larger study carried out in an emerging and high-intensity *S. mansoni* focus in the Senegal River valley, Piquet and colleagues reported an overall CR of 76.1% and an ERR of 88.1% after administration of two 40 mg/kg doses of PZQ spaced by 4 weeks (Picquet et al., 1998). The GM faecal egg count was considerably higher than in the current study conducted in Niger (478 EPG *vs.* 125 EPG). In Côte d'Ivoire, two doses of PZQ (60 mg/kg given as split dose of 30 mg/kg within 3 hours plus a second dose of 40 mg/kg 5 weeks later) administered to *S. mansoni*-infected school-aged children resulted in a CR of 89.7% and an ERR of 92.5%. In this Côte d'Ivoire study, the pre-treatment GM faecal egg count was 161 EPG (Utzinger et al., 2000). In Uganda, Kabatereine et al. administrated two doses of PZQ 6 weeks apart in an area highly endemic for *S. mansoni* near Lake Albert (GM egg count >250 EPG), which resulted in CR and ERR 6 weeks after the second dosing of 69.1% and 99.6%, respectively (Kabatereine et al., 2003). The low CRs and ERRs against *S. mansoni* following two closely spaced doses of PZQ reported here is of concern and we recommend follow-up studies that include molecular methods that might help to elucidate strain-specific sensitivity/tolerance to PZQ.

Interestingly, the treatment efficacy against *S. haematobium* and *S. mansoni* showed no statistically significant difference when comparing children with a single species or a mixed species infection, although samples sizes were arguable small. Previous studies have shown that treatment efficacy is influenced by pre-treatment infection intensity, and the current study

suggest that additional research is warranted to elucidate the potential role of the host's co-infection status pre-treatment.

Re-infection patterns of schistosomiasis are governed by multiple factors, such as local ecology and epidemiology (e.g. temporary or permanent water bodies), human water-contact patterns, pre-treatment infection intensity and schistosome species (Kahama et al., 1999; Ernould et al., 2004). In general, re-infection with *S. mansoni* occurs more rapidly than *S. heamatobium*, as observed in several studies in mixed infection foci (Daffalla and Fenwick, 1982; Ernould et al., 2004). N'Goran et al. followed a cohort of schoolchildren over a 24-month period in four villages of south-central Côte d'Ivoire, which allowed detailed investigation of re-infection patterns with *S. haematobium* (N'Goran et al., 2001). The CR in the Côte d'Ivoire study, using a single 40 mg/kg dose of PZQ, was acceptable (82% 4 weeks post-treatment). Six months post-treatment, the observed prevalence was 63% in Taabo Village (GM egg count 0.4 eggs/10 ml of urine), 49% in Batera (GM egg count 3.2 eggs/10 ml of urine), 14% in Bodo (GM egg count 1.4 eggs/10 ml of urine) and 10% in Assinzé (GM egg count 1.6 eggs/10 ml of urine). At the 12-month follow-up, the prevalence reached pre-treatment level (85%) in Taabo Village, but remained low in the other three settings. In the present study, re-infection with *S. haematobium* was higher along the Niger River where transmission is permanent than in villages located in close proximity to temporary ponds where the transmission is seasonal although the pre-treatment infection intensities were comparable.

In the current study, we monitored adverse events, both acute (within 4 hours) and solicited (within 24 hours), following PZQ administration. Three issues are worth highlighting. First, no severe adverse events were observed. Second, adverse events were transient; most of them had disappeared within the 4-24 hours post-treatment window. Third, adverse events were more frequent after the first dose of PZQ compared to the second one 3 weeks later. Indeed, while 32.9% of the treated children reported mild and transient adverse events after the first dose of PZQ, only 1.5% did so after the second dose. Twenty-four hours after administration of a single 40 mg/kg oral dose of PZQ in an area endemic for *S. mansoni* in western Côte d'Ivoire, Raso and colleagues observed adverse events in 12.5% of the participants (Raso et al., 2004). Another study carried out in south-central Côte d'Ivoire, where *S. haematobium* is endemic, reported adverse events among 33.3% and 13.3% of children after the first and second dose of PZQ, respectively (N'Goran et al., 2001). Our study

therefore confirms that PZQ-related adverse events are associated with pre-treatment infection intensity.

Abdominal pain, nausea and headache were the most frequent symptoms in the current study, as well as in previous investigations. Considerably higher frequencies of adverse events were reported in Kenya (Olds et al., 1999) and Ethiopia (Berhe et al., 1999). Briefly, in Kenya, 88% of individuals infected with *S. mansoni* and 65% of participants infected with *S. haematobium* reported adverse events, most of which occurred 4-6 hours after PZQ administration (Olds et al., 1999). In Ethiopia, the frequency of adverse events 4-6 hours post-treatment was 14.7%, whereas 91.5% of the participants reported adverse events within 24 hours, mainly abdominal pain and diarrhoea (Berhe et al., 1999). However, no mention of the feeding status of the participants prior to treatment was made. There is growing consensus that food intake prior to PZQ administration can lower the frequency and severity of adverse events, and hence improve acceptance of the treatment by community members.

In conclusion, two 40 mg/kg oral doses of PZQ given 3 weeks apart are efficacious against *S. haematobium* in a highly endemic area of western Niger. However, low CRs and ERRs were observed against *S. mansoni* in the two mixed-infection villages. Our findings raise concern about mounting PZQ tolerance against *S. mansoni*, and hence warrant detailed follow-up studies, including laboratory investigations and rigorous monitoring of PZQ efficacy within the frame of the national schistosomiasis and other NTD control programmes.

5.6. Conflicts of interest

None declared.

5.7. Authors' contributions

AG, ANG, JPW and JU contributed to the concept and the design of the study protocol. AG, MSL, NB, AD, BS, ANG, RL and HS carried out the field work. AG performed analysis and interpretation of the data. AG, assisted by JU, prepared the first draft the manuscript. JPW and AF assisted with the revision of the manuscript. All authors read and approved the final manuscript. AG and JU are guarantors of the paper.

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6. Safety and efficacy of praziquantel syrup (Epiquantel®) against *Schistosoma haematobium* and *Schistosoma mansoni* in preschool-aged children in Niger

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6.1. Abstract

Given the characteristic age-prevalence curve of *Schistosoma* infection, preventive chemotherapy with praziquantel is primarily targeted at school-aged children, whilst, in highly endemic areas, other high-risk groups might be included for regular treatment. Nevertheless, schistosomiasis can affect children well before they reach school-age, but this population group is usually excluded from preventive chemotherapy. We assessed the safety and efficacy of praziquantel syrup (Epiquantel®) in preschool-aged children in three villages of Niger. Children aged ≤72 months provided multiple urine and stool samples that were microscopically examined using standard protocols. *Schistosoma*-positive children were treated with praziquantel syrup at a dose of 40 mg/kg after a meal of millet porridge. Children remained under medical supervision for four hours and adverse events were recorded. Additionally, a questionnaire was administrated to the mothers/guardians 24 hours post-treatment for further probing of adverse events. Treatment efficacy was evaluated three and six weeks post-treatment using multiple stool and urine samples. A third of the 243 treated children reported adverse events within four hours, whilst a further 6.2% reported adverse events upon probing 24 hours post-treatment. Abdominal pain, bloody diarrhoea and sleepiness were the most common adverse events, but these were transient and self-limiting. Praziquantel syrup showed moderate-to-high efficacy against *S. haematobium* with egg reduction rates of 69.4% and 71.2% three and six weeks post-treatment and cure rates of 85.7% (95% confidence interval (CI) 79.7-90.5%) and 94.9% (95% CI 90.5-97.6%), respectively. Considerably lower cure and egg reduction rates were observed against *S. mansoni* (e.g. cure rate at 6-week post-treatment follow-up was only 50.6% (95% CI 39.9-61.2%). Concluding, praziquantel syrup is well tolerated in preschool-aged children with moderate-to-high efficacy against *S. haematobium*, but considerably lower efficacy against

S. mansoni in Niger. A larger study is warranted to investigate the observed differences in species-specific susceptibilities and to assess operational issues and community-effectiveness.

Keywords: Praziquantel, syrup formulation; Safety; Efficacy; Preschool-aged children; schistosomiasis; *Schistosoma mansoni*; *Schistosoma haematobium*; Niger

6.2. Introduction

Human schistosomiasis continues to constitute a major public health problem, particularly in sub-Saharan Africa (Utzinger et al., 2009; Gray et al., 2011; Rollinson et al., 2012). Patent *Schistosoma* infection is characterised by the presence of parasite eggs in urine (*Schistosoma haematobium*) or faeces (*Schistosoma mansoni* and other species). The long-term consequences of *Schistosoma* infection are bladder and liver fibrosis, portal hypertension, kidney failure and cancer of the bladder (Gray et al., 2011; Gryseels, 2012). Moreover, *S. haematobium* can cause genital bleeding, extra uterine pregnancies, and sterility in women and might enhance the risk of HIV transmission (Stoever et al., 2009; Kjetland et al., 2012).

In Niger, it is currently estimated that between 1.7 and 4.5 million people are at risk of schistosomiasis (Schur et al., 2011). The main transmission areas are concentrated within irrigated fields of the Niger River valley (Garba et al., 2006). In certain villages, the prevalence of infection can exceed 90% in school-aged children (Garba et al., 2010b). Since 2004, a national programme for the control of schistosomiasis and soil-transmitted helminthiasis was implemented by the Ministry of Health. In line with recommendations by the World Health Organization (WHO), the main objective is to reduce morbidity due to schistosomiasis and soil-transmitted helminthiasis by regularly treating at least 75% of school-aged children and other high-risk groups where the prevalence of infection exceeds 50% (WHO, 2002; Garba et al., 2006). By focusing the treatment primarily on the school-aged population, this strategy excludes younger children from praziquantel-based preventive chemotherapy. However, previous studies have shown that in highly endemic areas, women are accompanied by their young children when they spend time at water contact points where schistosomiasis transmission takes place (Stothard and Gabrielli, 2007; Garba et al., 2010a). Indeed, several studies carried out in Niger and elsewhere in Africa showed high prevalence

of *Schistosoma* infection in preschool-aged children (Garba et al., 2010a; Dabo et al., 2011; Stothard et al., 2011; Coulibaly et al., 2012; Ekpo et al., 2012). For example, in the villages of Falmado and Diambala in western Niger, we found *S. haematobium* prevalence of 50.5% and 60.5%, respectively, in children below the age of 5 years. Worryingly, one 6-month-old child already exhibited a patent infection. Moreover, in Diambala where *S. haematobium* and *S. mansoni* co-exist, the prevalence of *S. mansoni* in the same group of children was 43.8%, whereas 28.6% of the children had a mixed *S. haematobium-S. mansoni* infection (Garba et al., 2010a).

Praziquantel is widely used. Indeed, an estimated 33.5 million treatments were administered in 2010 alone (WHO, 2012). In general, praziquantel is well tolerated and can be used in pregnant and lactating women (Olds, 2003). Hence, the WHO extended its recommendations to also treat pregnant and lactating women (Savioli et al., 2009). It is therefore conceivable that infants are in contact with praziquantel by the intermediary of the mother's milk when lactating mothers are treated (Olds, 2003). However, the lack of information on morbidity, safety and efficacy of praziquantel in preschool-aged children are important reasons evoked for non-integration of this age group in preventive chemotherapy control programmes (Stothard and Gabrielli, 2007). The absence of an adapted oral formulation for the youngest children (e.g. syrup) is an additional reason for the non-inclusion of this age group in preventive chemotherapy (WHO, 2007; Keiser et al., 2011). Indeed the use of tablets to deworm young children, especially those aged below 2 to 3 years, might lead to chocking, which has resulted in fatalities during large-scale deworming campaigns, as reported from Ethiopia and Madagascar (Yewale and Dharmapalan, 2012). Recent studies focussing on the epidemiology and control of schistosomiasis in preschool-aged children used crushed praziquantel tablets, mixed with water or a juice, before oral administration (Odogwu et al., 2006; Sousa-Figueiredo et al., 2009; Garba et al., 2010a; Coulibaly et al., 2012).

Administration of crushed praziquantel tablets was efficacious and well tolerated (adverse events were mainly mild and self-limiting, disappearing within a few hours).

In Egypt, where praziquantel syrup (Epiquantel®) is available, children under the age of 5 years have been treated with this formulation. However, limited information exists on safety and efficacy. Hence, the WHO provided different Ministries of Health and research groups with a syrup formulation to assess its safety, efficacy and compliance issues. A study carried out in Uganda found that praziquantel syrup was equally efficacious than crushed praziquantel tablets among children below the age of 5 years (cure and egg reduction rates were above 80% and similar in both groups) with no difference in adverse events and non-compliance profiles (Navaratnam et al., 2012). The objective of the current study was to assess the safety and efficacy of Epiquantel® in preschool-aged children in Niger in order to provide additional evidence for the treatment of this age group with praziquantel as part of the ongoing preventive chemotherapy control programmes implemented in highly endemic areas.

6.3. Materials and methods

6.3.1. Study design and investigational drug

We present an analytical intervention study aiming to assess the safety and efficacy of praziquantel syrup in preschool-aged children infected with *S. haematobium* and/or *S. mansoni*. In this cohort study, children with patent *Schistosoma* infection were treated and followed-up 3 and 6 weeks post-treatment.

The investigational drug is Epiquantel® (batch no. 087684), an oral suspension of praziquantel presented in a 15 ml bottle with a total dose of 1,800 mg. The syrup is manufactured by Egyptian International Pharmaceutical Industries Co. (EIPICO).

6.3.2. Study sites

The study was carried out in three villages of Niger: Ndounga, Bonfeba and Zamakoira. Ndounga (geographical coordinates 13°21'34.9" N latitude and 2°14'51" E longitude) is located in the department of Kollo (Tillabéri region), approximately 20 km east of the capital town Niamey, and is situated in close proximity to an irrigated rice perimeter. Other crops produced here are millet, groundnut and beans. Water is supplied via several individual wells, drilling and a small drinkable water conveyance. There are three schools and a health centre in Ndounga. The only human schistosome species present is *S. haematobium*. A pre-selection survey conducted in March 2010 in school-aged children found a very high prevalence of 83.3%. A door-to-door census carried out by our team in early 2010 revealed a population of 1,207 inhabitants. Large-scale administration of praziquantel has been carried out in 2004, 2005, 2007 and 2009 by the Ministry of Health, usually reaching high coverage.

Bonfeba (14°22'32.52" N, 1°12'43.19" E) is located 45 km in the west of Tillabéri. During our March 2010 census, we determined the population at 2,106 inhabitants. The economic activity is mainly based on rice cultivation, fishing and livestock rearing. Irrigation canals have been identified as the main transmission sites for schistosomiasis. A pre-survey carried out in school-aged children in March 2010 found a prevalence of 66.7% for *S. mansoni* and 21.1% for *S. haematobium*. There are three primary schools and one health centre. Water supply is poor; indeed, the village counts only one drilling. Preventive chemotherapy using praziquantel has been implemented between 1997 and 2000 by the Niger River Valley Bilharzia Control Project (Garba and Alarou, 2000) and again in 2004, 2005,

2007 and 2009 by the national control programme supported by the Schistosomiasis Control Initiative (Fenwick et al., 2009).

Zamakoira (13°42'36.72" N, 1°43'10.56" E) is located in Kollo department. Our March 2010 census revealed a population of 1,140 people. The main activities of the population are irrigated rice farming with two production cycles per year. Additionally, in the rainy season, millet is cultivated. The village has one primary school and one health centre. The main water sources are a small river crossing the village and two pumps. A survey carried out in May 2010 found a prevalence of 42.5% for *S. haematobium* among school-aged children. The village received preventive chemotherapy with praziquantel at the same time as Bonfeba.

6.3.3. Study population

After completing village censuses in March 2010, we invited all the mothers/guardians who had been registered with children aged ≤72 months to participate in our study. The following inclusion criteria were employed: (i) age ≤72 months; (ii) living in the village for at least six months prior to the start of the study; (iii) written informed consent form signed by parents or guardians; (iv) infected with *S. haematobium*, or *S. mansoni* or both species concurrently; (v) good health as determined by a medical doctor; (vi) no anthelminthic treatment one month before the start of the study; and (vii) no participation in any other clinical trial.

6.3.4. Procedures

6.3.4.1. Questionnaire survey and clinical examination

The exact age of the children, their medical background and medication history were obtained from the health booklet of the children. For children presenting without this health

booklet, a questionnaire was administrated to the mothers/guardians to collect this essential set of information.

A clinical examination was performed by a physician to assess the general health status of the child. Based on these findings, it was decided whether or not a child could be included in the praziquantel syrup safety and efficacy study. For participating children, their weight was determined using a digital scale (nearest 0.1 kg) and their axillary temperature determined with a digital thermometer (nearest 0.01 °C).

6.3.4.2. Parasitological examination of urine and stool samples

Eligible children were invited to provide three urine samples over consecutive days in each of the three cross-sectional surveys that were processed using standard protocols. In brief, urine samples were collected between 10:30 and 14:00 hours and subjected to a filtration method. Urine samples were vigorously shaken and 10 ml were filtered using 13-mm diameter Nucleopore filters. The filters were placed on microscope slides, a drop of Lugol's iodine added, before examination under a microscope by experienced laboratory technicians. The number of *S. haematobium* eggs per slide was counted and recorded for each child separately.

Three stool samples were collected over consecutive days at baseline in all three villages and for the two follow-ups only in Bonfeba (sole village where *S. mansoni* occurs) and subjected to the Kato-Katz technique. We prepared 41.7 mg thick smears from each stool sample (Katz et al., 1972).

Intensity of schistosome infections were classified according to WHO guidelines (WHO, 2002). Hence, for *S. haematobium*, intensity was stratified into light (1-49 eggs/10 ml of

urine) and heavy infections (≥50 eggs/10 ml of urine). The intensity of *S. mansoni* infection was classified as light (1-99 eggs per gram of stool (EPG), and moderate/heavy infection (≥100 EPG).

6.3.4.3. Treatment and assessment of adverse events

A dose of 40 mg/kg of praziquantel was administered to children identified with patent *Schistosoma* infection. All children were given a millet-based wafer and porridge prior to treatment, in order to enhance praziquantel bioavailability (Castro et al., 2000).

Praziquantel syrup bottles were vigorously shacked to homogenize the solution. The exact quantity of medicine was taken with a millilitre scale pipette (Figure 6.1a). The dose was then diluted with bottled water in a cup and given to the children by their mothers/guardians (Figure 6.1b). In case vomiting occurred within one hour of drug administration, a second dose was administered. Children remained under medical supervision for a period of four hours. Acute adverse events were recorded and appropriate measures taken by the study physician. After this 4-hour direct surveillance period, mothers/guardians and their children were allowed to return home. Mothers/guardians were encouraged to report adverse events that occurred within 24 hours post-treatment.

Fig. 6.1. Dosing the required amount (40 mg/kg) of praziquantel syrup (A) and administration of the syrup by the child's mother (B)

6.3.5. Ethical consideration

Authorization to undertake the study was obtained from the national ethics committee of Niger (no. 07/2010/CCEN). Village authorities and local health authorities were informed about the study. The objectives, procedures, potential risk and benefits were explained in the local language, using lay terms, to all the mothers/guardians. Written informed consent was obtained from all the participating mothers/guardians. It was emphasised that participation was voluntary, and hence children could be withdrawn from the study without further obligation. At the end of the study, all participating children were again treated with praziquantel syrup at 40 mg/kg.

6.3.6. Statistical analysis

Data were collected on paper forms and double-entered and analysed using EpiInfo version 3.5.3 (Centers for Disease Control and Prevention; Atlanta, USA). Only those children who were found positive for *S. haematobium* and/or *S. mansoni* at the baseline cross-sectional survey and who were given praziquantel syrup were considered for analysis (per-protocol analysis).

The proportion of children experiencing adverse events within four hours (assessed by the study physician) and within 24 hours (reported by mothers/guardians) was calculated. Cure rate (CR) and egg reduction rate (ERR) 3 and 6 weeks post-treatment were the primary efficacy measures. CR was defined as the proportion of individuals infected either with *S. haematobium* or *S. mansoni* at baseline who became egg-negative 3 or 6 weeks after the treatment. ERR was defined as the percentage reduction of the geometric mean egg count for the positive individuals. The geometric mean was calculated as the antilogarithm of the mean of the log-transformed egg counts only for *Schistosoma*-positive individuals.

P-values <0.05 were considered to indicate statistical significance. We compared proportions using Pearson's χ^2 with Yates correction. Geometric mean egg counts among different groups were compared using Anova or Kruskal-Wallis test, as appropriate.

6.4. Results

6.4.1. Characteristics of the study population

Overall, 243 children met our inclusion criteria, i.e. they were ≤72 months of age, lived in the village for at least 6 months before the study, had written informed consent by parents/guardians, were infected with either *S. haematobium*, or *S. mansoni* or both species concurrently, they were of good general health, did not receive anthelminthic treatment within

the past month and did not participate in other trials, and hence they were treated with praziquantel syrup. The largest group of children came from Bonfeba, the village where *S. haematobium* and *S. mansoni* co-exist (43.2%). There were significantly more boys than girls (138 *versus* 105, χ^2=4.45, p=0.035). The mean age of the children was of 41 months (standard deviation (SD), 16 months) ranging from 1 to 67 months. The mean weight of the children was 12.6 kg (range, 5.1-18.2 kg). The number of children with a *S. haematobium* mono-infection was 147, while 78 had a *S. mansoni* mono-infection. Eighteen children were identified with mixed infections.

Table 6.1
Characteristics of the surveyed preschool-aged children, stratified by study setting

Village	Female	Male	Total
Bonfeba	48 (45.7%)	57 (54.3%)	105
Ndounga	24 (42.9%)	32 (57.1%)	56
Zamakoira	33 (40.2%)	49 (59.8%)	82
Total	105 (43.2%)	138 (56.8%)	243

6.4.2. Safety of praziquantel syrup

No serious adverse events were observed throughout the study. The overall proportion of children experiencing at least one adverse event after treatment was 34.2%. Most of the adverse events occurred within four hours after drug administration (32.5%), while the proportion of adverse events 24 hours post-treatment was considerably lower (6.2%). We found no difference in the occurrence of adverse events in relation to age (χ^2=0.11, p=0.991 for the occurrence of at least one adverse event).

Table 6.2
Frequency (%) of adverse events among preschool-aged children in Niger treated with praziquantel syrup, according to the time of occurrence stratified by children's age

	1-23 months	**24-35 months**	**36-59 months**	**60-67 months**	**Total**
Number included	33	35	120	55	243
Adverse events (within 4 hours post-treatment)	36.4%	34.3%	30.8%	32.7%	32.5%
Adverse events (between 4 and 24 hours post-treatment)	3.0%	8.6%	5.0%	9.1%	6.2%
At least one adverse event	36.4%	34.3%	33.3%	34.5%	34.2%

The most common adverse event was abdominal pain (30.6%), followed by bloody diarrhoea (16.2%) and sleepiness (15.3%). The proportion of children vomiting was 7.1%. Three out of the 18 reported bloody diarrhoeal episodes occurred within four hours post-treatment, as reported to the study physician. Thirteen children reported fever, all occurring within the first four hours post-treatment.

6.4.3. Efficacy of praziquantel syrup against S. haematobium

The results of the efficacy of praziquantel syrup against *S. haematobium* are summarised in Tables 6.3 and 6.4. At baseline, 165 children were infected with *S. haematobium*, most of them with light intensities (1-49 eggs/10 ml of urine), whereas 12.7% showed heavy infections (≥50 eggs/10ml of urine). In Bonfeba, all of the *S. haematobium* infections were of light intensity. The proportion of heavy infections was higher in Ndounga (17.9%) than in Zamakoira (13.4%) with no statistically significant difference (χ^2=0.36, p=0.549). The infection intensity varied significantly according to village (Anova, F=6.52, p=0.001). The overall geometric mean egg count per child was 5.8 eggs/10 ml of urine. A higher geometric

mean egg count was found in Ndounga (9.2 eggs/10 ml of urine) compare to Zamakoira (5.5 eggs/10 ml of urine). The baseline geometric mean egg count and the proportion of heavy infection was higher among children aged ≥60 months that their younger counterparts (Table 6.4), but no significant difference was observed between these two age classes (Anova, F=0.57, p=0.63). There was also no difference in the infection intensity between sex (χ^2=1.02, p=0.310) during the baseline cross-sectional survey.

Three weeks post-treatment, the overall CR against *S. haematobium* was 85.7% (95% confidence interval (CI) 79.7-90.5%) (Table 6.3). It was 100% in Bonfeba, 80.8% in Ndounga and 84.1% in Zamakoira. The overall geometric mean ERR was 69.4%, ranging between 61.0% (Zamakoira) and 100% (Bonfeba).

Six weeks after treatment, observed CRs were slightly higher in all the three villages. The global CR was 94.9% (95% CI 90.5-97.6%). It was 100% in Bonfeba, 97.6% in Zamakoira and 88.2% in Ndounga. The overall geometric mean ERR was 76.6% with a geometric mean egg count of 1.4 eggs/10 ml of urine.

Table 6.3

Efficacy of praziquantel syrup against *S. haematobium* infection in preschool-aged children in Niger stratified by setting

Characteristics	Study setting			Total
	Bonfeba	Ndounga	Zamakoira	
Baseline				
Number (%) of children included	27 (16.1)	56 (33.3)	82 (50.6)	165 (100.0)
Number (%) of children with light infection (1-49 eggs/10 ml of urine)	27 (100)	46 (82.1)	71 (86.6)	144 (87.3)
Number (%) of children with heavy infection (≥50 eggs/10 ml of urine)	0 (0.0)	10 (17.9)	11 (13.4)	21 (12.7)
Geometric mean egg count per 10 ml of urine	2.3	9.2	5.2	5.6
Three weeks post-treatment				
Number (%) of children examined	27 (100.0)	52 (92.9)	82 (100.0)	161 (97.6)
Number of children cured (CR, %)	27 (100.0)	42 (80.8)	69 (84.1)	138 (85.7)
Geometric mean egg count per 10 ml of urine	0.0	1.5	2.0	1.7
Geometric mean egg reduction rate (ERR, %)	100.0	83.6	61.0	69.4
Six weeks post-treatment				
Number (%) of children examined	25 (92.6)	51(91.1)	81 (98.8)	157 (95.2)
Number (%) of children cured (CR, %)	25 (100.0)	45 (88.2)	79 (97.5)	149 (94.9)
Geometric mean egg count per 10 ml of urine	0.0	1.5	1.0	1.4
Geometric mean egg reduction rate (ERR, %)	100.0	83.6	80.8	71.2

Table 6.4

Efficacy of praziquatel against *S. haematobium* in preschool-aged children in Niger, stratified by age

Characteristics	Age (months)				Total
	1-23	24-35	36-59	60-67	
Baseline					
Number (%) of children included	21 (12.7)	26 (15.8)	83 (50.3)	35 (21.2)	165 (100.0)
Light infection (1-49 eggs/10 ml of urine)	20 (95.2)	23 (88.5)	75 (90.4)	26 (74.3)	144 (87.3)
Heavy infection (≥50 eggs/10ml of urine)	1 (4.8)	3 (11.5)	8 (9.6)	9 (25.7)	21 (12.7)
Geometric mean egg count per 10 ml of urine	2.24	4.29	5.28	12.98	5.55
Three weeks post-treatment					
Number (%) of children examined	21 (100.0)	24 (92.3)	82 (98.8)	34 (97.1)	161 (97.6)
Number (%) of children cured (CR, %)	18 (85.7)	23 (95.8)	70 (85.4)	27 (79.4)	138 (85.7)
Geometric mean egg count per 10 ml of urine	1.4	3.0	1.7	1.7	1.7
Geometric mean egg count reduction rate (ERR, %)	37.1	30.1	67.2	86.9	69.4
Six weeks post-treatment					
Number (%) of children examined	19 (90.5)	24 (92.3)	81 (97.6)	33 (94.3)	157 (95.2)
Number of children cured (CR, %)	18 (94.7)	23 (95.8)	76 (93.8)	32 (97.0)	149 (94.9)
Geometric mean egg count per 10 ml of urine	1.0	1.0	1.6	1.0	1.4
Geometric mean egg reduction rate (ERR, %)	55.4	76.7	68.9	92.3	71.2

6.4.4. Efficacy of praziquantel syrup against S. mansoni

The results of the efficacy of praziquantel syrup against *S. mansoni* are summarised in Table 6.5. At baseline, 96 children were infected with *S. mansoni*. Most of the infections were of light intensity (61.5%). Children aged 1-23 months showed the highest proportion of light infection, while children aged 36-59 months had the highest proportion of moderate and heavy infection (46.8%). The overall geometric mean egg count was 71.8 EPG.

Three weeks post-treatment, the overall CR was 75.0% (95% CI: 65.1-83.2%) with a geometric mean ERR of 66.7%. The CR was higher in children aged 1-23 months compared to their older counterparts (83.3% *versus* 66.7%).

Six weeks after treatment, a considerably lower overall CR was determined (50.6%, 95% CI 39.9-61.2%) but it remained stable in the youngest children (90.0% in children aged 1-23 months). The geometric mean ERR six weeks post-treatment was low (18.5%).

Table 6.5

Efficacy of praziquantel against *S. mansoni* in preschool-aged children in Niger, stratified by age

Characteristics	Age (months)				Total
	1-23	24-35	36-59	60-67	
Baseline					
Number (%) of children included	14 (14.6)	12 (12.5)	47 (48.9)	23 (24.0)	96 (100.0)
Number (%) of children with light infection (1-99 EPG)	12 (85.7)	8 (66.7)	25 (53.2)	14 (60.9)	59 (61.5)
Number (%) of children with moderate and heavy infection (≥100 EPG)	2 (14.3)	4(33.3)	22(46.8)	9 (39.1)	37 (38.5)
Geometric mean egg count (EPG)	44.6	64.4	73.2	97.7	71.8
Three weeks post-treatment					
Number (%) of children examined	12 (85.7)	12 (100.0)	43 (91.5)	21(91.3)	88 (91.7)
Number of children cured (CR, %)	10 (83.3)	7 (58.3)	35 (81.4)	14 (66.7)	66 (75.0)
Geometric mean egg count (EPG)	13.9	53.3	21.8	18.2	23.9
Geometric mean egg reduction rate (ERR, %)	68.9	17.2	70.2	81.3	66.7
Six weeks post-treatment					
Number (%) of children examined	10 (71.4)	10 (83.3)	43(91.5)	20 (86.9)	83 (86.5)
Number of children cured (CR, %)	9 (90.0)	3(30.0)	22 (51.2)	8 (40.0)	42(50.6)
Geometric mean egg count (EPG)	24.0	74.0	51.1	69.1	58.5
Geometric mean egg reduction rate (ERR, %)	46.2	-14.9	30.2	29.2	18.5

6.4.5. Comparison of treatment efficacy according to Schistosoma *species*

We found significantly higher CRs of praziquantel syrup against *S. haematobium* compared to *S. mansoni*. At the 3-week post-treatment follow-up, the respective CRs against *S. haematobium* and *S. mansoni* were 85.7% and 75.0%, owing to a statistically significant difference (χ^2=4.41, p=0.018). At the 6-week post-treatment follow-up, the difference between the CRs against *S. haematobium* and *S. mansoni* were even more pronounced (94.9% *versus* 50.6%; χ^2=65.58, p<0.001).

6.5. Discussion

Inclusion of preschool-aged children in preventive chemotherapy against schistosomiasis might be justified in specific high-risk areas (e.g. settings in close proximity to large dams and irrigation systems), as infection prevalence and morbidity in this age group might already be considerable. Severe morbidity due to schistosomiasis results from an accumulation of infections and consequently high worm loads, and hence timely treatment of young children might prevent the development of irreversible morbid sequelae. Bloody diarrhoea due to *S. mansoni* and haematuria due to *S. haematobium* may cause anaemia, malnutrition and delayed physical and cognitive development in young children (Gray et al., 2011; Gryseels, 2012). These negative consequences might be avoided by early treatment with praziquantel. Moreover, with a shift from morbidity control to transmission interruption and ultimately local elimination (King et al., 2006; Bergquist et al., 2009; Stothard et al., 2009; Rollinson et al., 2012), the inclusion of preschool-aged children into preventive chemotherapy campaigns must be considered, alongside improvement of sanitation, clean water and hygiene behaviour to curb transmission (Utzinger et al., 2009).

However, the extent and impact of schistosomiasis in preschool-aged children remains to be further elucidated. Additionally, there is a paucity of quality data on the safety and efficacy

of praziquantel in preschool-aged children (Keiser et al., 2011), and a syrup formulation has only been available in Egypt. These are reasons that might explain why young children are currently excluded from preventive chemotherapy. With the exception of a recent paper pertaining to the safety and efficacy of praziquantel syrup against *S. mansoni* in a group of preschool-aged children in Uganda (Navaratnam et al., 2012), preceding work determined the efficacy of crushed praziquantel tablets administered to preschool-aged children. In these studies, investigators usually used 600-mg tablets of praziquantel, crushed them between two spoons and mixed the powder with water or a juice to mask the bitter taste of the drug before administration (Doenhoff et al., 2008; Meyer et al., 2009). This approach is not only time consuming, but some brands of praziquantel tablets are difficult to cut into two, three or four pieces in order to obtain the appropriate dosage of 40 mg/kg. Of note, 600-mg praziquantel tablets are the most widely used formulation deployed by national control programmes (Doenhoff et al., 2008), whereas tablets of lower dose (e.g. 100 or 200 mg) are rarely used. Epiquantel® is a syrup brand produced and used in Egypt since 1998 (Talaat and Miller, 1998). The use of a downward extended dose-pole can help integrated preschool-aged children into preventive chemotherapy (Sousa-Figueiredo et al., 2012).

Reviewing the literature, we conjecture that our sample size comprising 243 *Schistosoma*-infected preschool-aged children is one of the largest focusing on the safety and efficacy of praziquantel syrup in this age group. In two previous studies done in Uganda, there were 155 (Odogwu et al., 2006) and 1,124 preschool-aged children included (Navaratnam et al., 2012), with *S. mansoni* prevalences of 7% and 26%, respectively. In the latter study, however, not all the children treated were infected. In another study in Nigeria, a sample of 167 preschool-aged children with an infection prevalence of 58.1% was included (Ekpo et al., 2010). Relatively large sample sizes were also included in Mali (Dabo et al., 2011) (n=338 children) and in another study in Uganda (Sousa-Figueiredo et al., 2009) (n=363 children).

Our baseline survey, using a reasonably sensitive diagnostic approach with triplicate urine filtration and triplicate Kato-Katz thick smear examinations revealed that 12.7% of the children harboured a heavy *S. haematobium* infection (≥50 eggs/10 ml of urine), while 38.5% of the children infected with *S. mansoni* showed a moderate or heavy infection (≥100 EPG).

Administration of praziquantel syrup was relatively straightforward. The precise syrup dose was taken with a pipette and poured in a small cup delivered with the Epiquantel® box and given to the mothers so that they could administer the drug to their children (Figure 6.1). As the syrup has a viscous consistency, the cup must be rinsed with water before use by the next child. We did not observe any immediate severe adverse events, such as false route or coughing. However, a third of the children experienced adverse events, most of which appeared within four hours and resolved within 24 hours. Indeed, while 32.5% of the treated children reported adverse events within four hours post-treatment, only 6.2% reported adverse events between four and 24 hours post-treatment. In a previous study administering two doses of praziquantel (standard tablets) within three weeks (40 mg/kg each) to school-aged children in Niger (Garba et al., 2012), the frequency of adverse events was similar (32.9%). Previous observations of abdominal pain, bloody diarrhoea and sleepiness being the most common adverse events in schoolchildren corroborate with findings reported here in preschool-aged children. In contrast, in Uganda, fewer adverse events were reported after praziquantel treatment in *S. mansoni*-infected preschool-aged children (2.6% reported feeling ill 24 hours post-treatment) (Sousa-Figueiredo et al., 2009). Importantly though, not all of the children were infected; the prevalence of infection was 44.3% with a geometric mean egg count of 6.1 EPG. In another study carried out in Uganda where a low infection prevalence of *S. mansoni* was observed, no adverse events were recorded within 24 hours post-treatment (Odogwu et al., 2006). In our study, by design, only *Schistosoma*-infected children were included and the geometric mean egg count was more than 10-fold higher (72.1 EPG).

In a recent study done in Mali, few adverse events were reported 24 hours post-treatment (3.3%) when using crushed praziquantel tablets in two villages where the *S. haematobium* prevalence was comparable to our study (i.e. 15.7% of heavy infection among children aged ≤5 years) (Dabo et al., 2011). The most frequent adverse events were sleepiness, dizziness and diarrhoea. In our study, children were fed before treatment, which enhances bioavailability of praziquantel (Castro et al., 2000). However, no mention of the feeding status of the participants prior to treatment was recorded in Uganda and Mali. In a recent multicentre praziquantel efficacy and safety trial among children aged 10-19 years (Olliaro et al., 2011), high frequencies of adverse events (78%) were reported within four hours, where results varied from one site to another from 66% to 92%. Praziquantel was administrated after food intake. In a study in Zimbabwe (Midzi et al., 2008), 54.3% of children reported single adverse events, whereas 11% reported two or more adverse events concurrently within 24 hours after administration of praziquantel at the standard dose of 40 mg/kg. Praziquantel was given with food and adverse events were actively probed by the survey team 24 hours after treatment. It is now commonly admitted that food intake prior to praziquantel not only enhances bioavailability, but also lowers the frequency and severity of adverse events. The difference in the higher proportion of adverse events we found might also stem from the fact that, in our study, children were closely monitored by a research team and clinicians within four hours after treatment. In some of the previous studies, mothers were asked to report any adverse events occurring within 24 hours post-treatment. Since adverse events are mainly transient, mothers might not have seen the necessity to report adverse events to the research team. Indeed, active probing for adverse events results in higher rates of reported adverse events (Olliaro et al., 2011).

Against *S. mansoni*, the CR and ERR were considerably lower compared to the results obtained with *S. haematobium*. We observed CRs of 75.0% and 50.6% after 3 and 6 weeks

post-treatment, respectively. While an ERR of 66.7% was found 3 weeks post-treatment, a much lower ERR of only 18.5% was observed at the 6 weeks post-treatment follow-up. In contrast, in Uganda, CR and ERR of 100% were observed after treating children <5 years of age with crushed praziquantel tablets at the same dose of 40 mg/kg (Sousa-Figueiredo et al., 2009). However these results have to be interpreted with caution, as the number of children with a confirmed *S. mansoni* infection in Uganda was low (i.e. only 28 children). Moreover, in the multicentre praziquantel trial against *S. mansoni* carried out in Brazil, Mauritania and Tanzania, high CRs (91.6-99.4%) and ERRs (89.2-91.9%) were observed (Olliaro et al., 2011). Of note, baseline geometric mean egg counts (278.3-813.5 EPG) were considerably higher than in the present study. In a previous study conducted in Niger, we observed a similar moderate response of *S. mansoni* to praziquantel (Garba et al., 2012). The CRs and ERRs were 51.7-58.8% in Diambala and 55.2-60.2% in Namarigoungou after two closely spaced doses of praziquantel, each given at 40 mg/kg to school-aged children. We speculate that the low response to praziquantel might be due to the high *S. mansoni* reinfection rates in this zone where the population is highly susceptible to the infection due to the emergence of *S. mansoni* (Garba et al., 2004). Six-month post-treatment reinfection rates of 38.1% (Diambala) and 74.1% (Namarigoungou) were observed in two villages located near our study site. Another reason could be the lower bioavailability of Epiquantel®. A study has shown a lower dissolution of Epiquantel® and Bilharzid®, compare to other brands of praziquantel resulting in a reduced efficacy against *S. mansoni*-infected mice (Botros et al., 2011).

In conclusion, treatment of children aged ≤72 months with praziquantel syrup is operationally feasible. Although adverse events occurred in about one-third of the children, these were mild and transient. Epiquantel® resulted in moderate-to-high efficacy against *S. haematobium*, but considerably lower CR and ERR were found against *S. mansoni*, particularly at the 6-week post-treatment follow-up. The latter observation warrants further follow-up investigations.

Moreover, financial implications of using a syrup formulation rather than tablets should be studied, alongside an individual diagnosis-treatment approach versus blanket treatment. In the interim, we suggest that, in areas where schistosomiasis remains highly endemic, preschool-aged children should be considered for inclusion in preventive chemotherapy, using crushed praziquantel tablets or, where available, syrup formulation.

6.6. Conflicts of interest

None declared.

6.7. Authors' contributions

AG and MSL designed the study. AG, MSL, AD, TA, MAA and AA carried out the field and laboratory work. AG performed analysis and interpretation of the data. AG, assisted by JU, prepared the first draft the manuscript. AEP and AF assisted with the revision of the manuscript. All authors read and approved the final manuscript. AG and JU are guarantors of the paper.

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7. Schistosomiasis and Soil-Transmitted Helminth control in Niger: cost-effectiveness of school-based and community distributed mass drug administration

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7.1. Abstract

Background

In 2004 Niger established a large scale schistosomiasis and soil-transmitted helminths control programme targeting school age children aged 5-14 years and adults. In two years 4.3 million treatments were delivered in 40 districts using school based and community distribution.

Method and Findings

Four districts were surveyed in 2006 to estimate the economic cost per district, per treatment and per schistosomiasis infection averted. The study compares the costs of treatment at start up and in a subsequent year, identifies the allocation of costs by activity, input and organisation, and assesses the cost of treatment. The cost of delivery provided by teachers is compared to cost of delivery by community distributers (CDD).

The total economic cost of the programme including programmatic, national and local government costs and international support in four study districts, over two years, was US$ 456,718; an economic cost/treatment of $0.58. The full economic delivery cost of school based treatment in 2005/06 was $0.76, and for community distribution was $0.46. Including only the programme costs the figures are $0.47 and $0.41 respectively. Differences at sub-district are more marked. This is partly explained by the fact that a CDD treats 5.8 people for every one treated in school.

The range in cost effectiveness for both direct and direct and indirect treatments is quantified and the need to develop and refine such estimates is emphasised

Conclusions

The relative cost effectiveness of school and community delivery differs by country according to the composition of the population treated, the numbers targeted and treated at school and in the community, the cost and frequency of training teachers and CDDs. Options analysis of technical and implementation alternatives including a financial analysis should form part of the programme design process.

7.2. Author Summary

Schistosomiasis and soil-transmitted helminth control programmes are important, relatively low cost means to improve the health of those affected, in particular rural school age children. It can also reduce schistosomiasis related morbidity in their later lives. The paper presents information on the implementation and costs of a large scale national programme in Niger.

The total economic cost per treatment was $0.58. This includes programme, government and international costs. Two systems, school based and community delivery were used to treat children and targeted adults. Contrary to findings in some countries we find that school based delivery is less cost effective than community delivery. This is due to the low proportion of the population targeted and treated by the school based system.

Treating adults as well as children increased the numbers treated and reduced the overall cost per treatment. Prevalence and infection is higher in children than adults and overall effectiveness in terms of infection averted is affected. The cost per infection averted is assessed for direct treatment and direct and indirect treatment effects. The study expands the evidence available for decision makers involved in programme planning and design, funding and implementation.

7.3. Introduction

Schistosomiasis is one of the most prevalent chronic infectious diseases found world-wide and is associated with anaemia, chronic pain, diarrhoea, and under nutrition. It is recognised as a major public health problem in many rural areas, particularly in school-age children. With affordable and sustained control measures morbidity and transmission can be decreased.

Robust studies on the implementation of large scale control of schistosomiasis and soil transmitted helminths (STH) are required to strengthen the evidence base on the cost-effectiveness and affordability of such investment [1]–[3]. In particular, evidence on effectiveness is needed to support the strategic planning for expanded treatment and global coverage as well as for national vertical and integrated Neglected Tropical Disease (NTD) programmes. The objectives of this study are to identify: the cost of the Mass Drug Administration (MDA) programme; the cost per person treated; and the costs of treatment as delivered by school based staff and community distributers.

A number of studies have identified the costs of targeted and MDA for schistosomiasis control [4]–[9]. These have, with the exception of [4], [9], provided empirical evidence of school based approaches. This paper provides the cost of MDA treatment and compares the costs of the school and community based distribution systems used. It assesses the evidence from other MDA programmes taking account of factors such as the level of school enrolment, coverage levels to consider the general guidelines that can be taken from these works

7.4. Description of the programme for mass drug administration in Niger

In 2004 Niger established a national programme to control schistosomiasis and soil-transmitted helminths (PNLBG) supported by the Schistosomiasis Control Initiative (SCI), funded by the Bill and Melinda Gates foundation [10]. Its objective in line with Resolution WHA54.19 was to treat 75% of school age children at risk of infection and in communities where prevalence is over 50% to also treat at risk adults. The purpose being to reduce the morbidity related to schistosomiasis infection to a level at which it would not constitute a public health problem [11].

The primary school net enrolment rate (NER) in 2004 in Niger was 41% (UNESCO UIS global education database Table 7.5, Enrolment ratios by International Standard Classification of Education (ISCED) level), lower in rural areas; and considerably less than the rate of 68% for Sub Saharan Africa (SSA). To achieve high treatment coverage in targeted school age children and at risk adults two treatment strategies, school-based and community-based distribution, were established. Treatment for *S. haematobium* was provided every two years in most endemic areas, and annually in high prevalence areas to reduce initial levels. School-based distribution was provided by trained teachers who distributed the drugs to students in the schools. Children not attending school could receive treatment either in the schools or from the Community Drug Distributor (CDD) at home or at another fixed treatment location.

The MDA programme was established and rolled out over 2 years from April 2004 across 40 districts in all 7 regions of the country, including the capital city Niamey. The programme activities were implemented progressively commencing in the Tilaberi and Dosso regions. In 2004/05, 1,627,828 treatments were delivered in 22 districts and in 2005/06 2,683,121 treatments were delivered in 40 districts. Figure 7.1 outlines the main MDA programme activities.

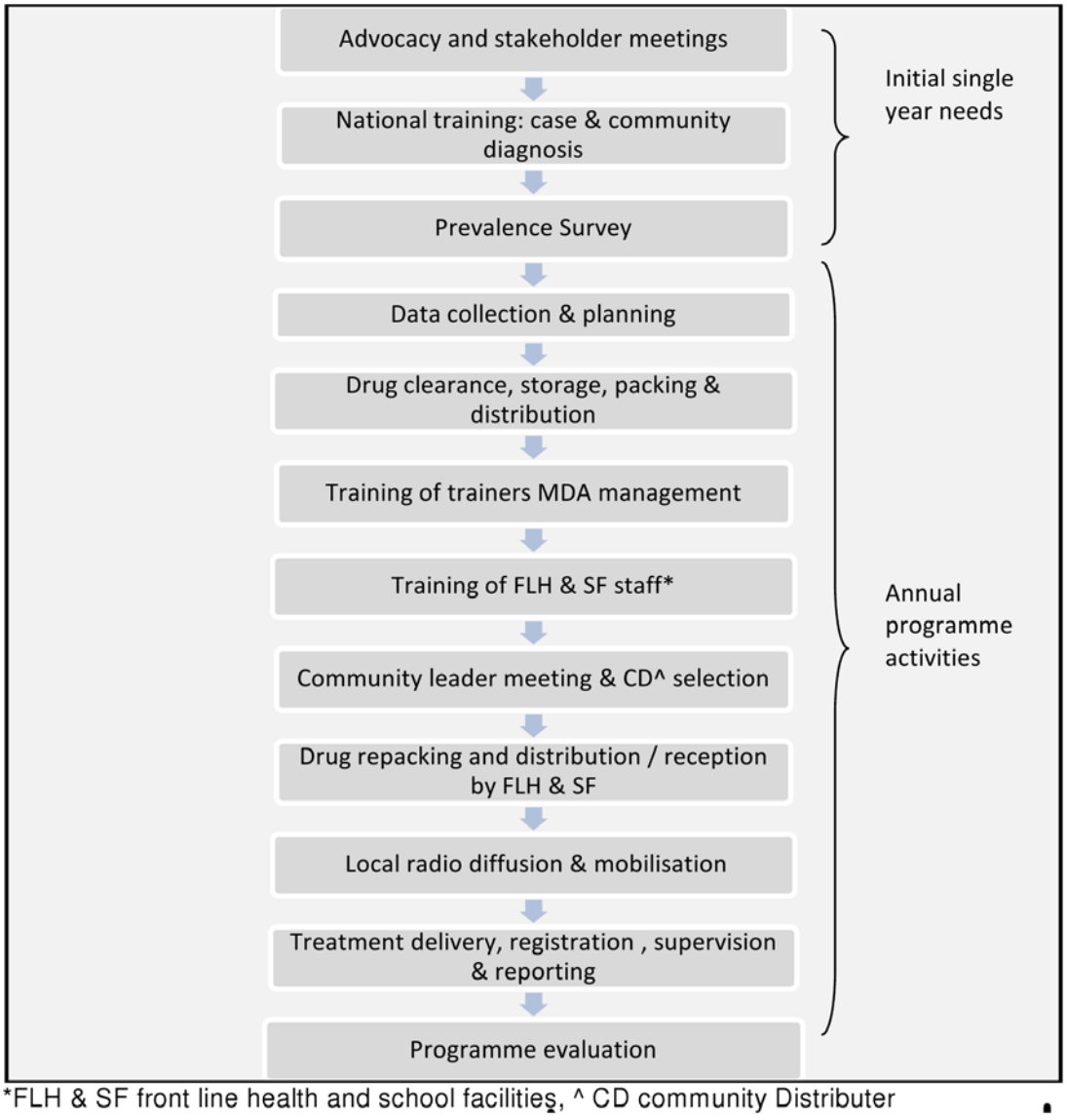

Figure 7.1. The main steps in the MDA programme. Figure 7.1 presents the component activities of the MDA process. Activities mainly occurring in the first year are shown as well as annual activities.

Initial meetings and agreement of the programme with the regional and district administrations were followed by a prevalence survey and mapping to prioritise areas for MDA. A national workshop and practical field sessions to develop capacity in the diagnosis of schistosomiasis was organised. Further capacity-building workshops and training for staff in organisation, management and implementation of MDA was provided to key district health and educational inspectorate staff in an initial national workshop. These staff then trained clinic staff, health workers and head teachers though district meetings. Training was provided

on the calculation of drug requirements, drug distribution organisation, the management of side effects and the reporting of results. Community and school-based drug distributors were trained in the use of dose poles (to determine drug dosage), and the completion of treatment forms.

The national programme developed, piloted, printed and delivered information, education and communication (IEC) materials for distribution to the districts. These materials included posters and a booklet for use in schools and communities as well as technical sheets for those administering the drugs. Drugs were procured centrally by SCI on behalf of countries which SCI supported in West and East Africa [12]. The drugs were sent directly from the National store to the districts. The districts and inspectorates repacked the drugs and IEC material for distribution to or collection by clinics and schools. Social mobilisation activities were undertaken at various administrative levels. National radio and television broadcasts were undertaken in three local languages and in French, organised by the PNLBG; local radio broadcasts were organised by the districts; village criers were organised by clinics to inform communities about the logistics of the MDA.

A rally to launch the campaign was undertaken and organised by an host region; it involved a day of speeches, dance and hospitality supported by national, regional and programme dignitaries and was broadcast on national radio and television.

Treatments were delivered at schools by teachers; CDDs provided treatment by going from door to door and at other fixed points supervised by clinic, district and regional staff. Technical and management support and supervision were provided to the districts by national staff.

At the end of the MDA unused drugs and monitoring reports were collected by national staff. A one day post MDA evaluation meeting was held in each participating region attended by national, regional and district staff. A summary of the partner roles and responsibilities is identified in Table 7.1.

Table 7.1. Roles and responsibilities in the Niger schistosomiasis and STH MDA.

National	Region & Department	Clinic, School, Community
• Advocacy meetings with national, regional and district health and education administrations	**Regional**	• Training by clinic nurse of community distributers
• Organisation of national prevalence survey	• Disbursement of funds to the districts, and	• The school head undertakes the training of school staff for school based MDA.
• Training for diagnosis	• Supervision of district MDA activities	• Engagement of village criers to publicise community MDA
• Drug clearance and reception	**District**	• Organisation of MDA drug delivery to the communities and MDA supervision of distributers
• Storage, repacking and delivery of drugs and materials to districts	• Training of primary school heads and clinic health staff;	• Supervision by Clinic Head Nurse of drug delivery by CDD and in schools by headmasters
• Central training of trainers for regional and district health and education staff	• Repacking and delivery of drugs and materials to the clinics and to the sector education authorities or schools	• Collation and reporting of treatments by clinic nurse and by head teacher to inspectorate
• Support for national campaign inaugural rally	• Supervision by district and inspectorate of drug delivery in communities and schools.	• Response to secondary effects reported to clinics initially
• Supervision, technical support of district MDA organisation & delivery	• District level radio emission and diffusion	• Disbursement of moneys for community MDA
• Collection of surplus drug supplies and coverage forms	• Disbursement of moneys to the clinics	
• Programme evaluation		
• National radio and television diffusion		

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7.5. Methods

A protocol for the cost and resource use study was agreed with Niger Ministries of Health and Education at national and local government level. Written informed consent to participate in the programme longitudinal surveillance and monitoring research was obtained from the children's parents or guardians, or head teachers according to the study protocol approved by St Mary Research Ethics Committee of Imperial College, UK, 2003, (EC No 03.36, R&D No: 03/SB/003E) and amended 2005 St Mary's (REC Ref: AM2003).

This was a retrospective study which covered a two year period from April 2004 to May 2006, including the first and second years of MDA and related programme activities in four health districts.

All data on first year costs at national, regional, district, and sub district levels were taken from the PNLBG accounts and receipts and records of staff missions or activities. Second year cost data for national and regional level activities were taken from receipts. District and sub district, school and community MDA resource use data for 2005 were collected in June 2006 through a retrospective survey. The four health districts: Kollo, Tera, Tilaberi, (Tilaberi region) and Gaya (Dosso region) are all located in the Niger River Valley, and were in the

first phase of implementation. The control programme had previously established sites for longitudinal monitoring of prevalence and morbidity in these districts.

The cost survey was designed to collect data on the time taken and resources used by district and sub district health staff, and by the education inspectorate and school staff in the 2005 MDA delivery. Questionnaires were designed and tested, and a 2 day training workshop was undertaken in 2006 to familiarise and train the schistosomiasis MDA district co-ordinators, responsible for the data collection.

The questionnaires covered the usage of: vehicles, fuel and other equipment and materials used in the MDA and in training, time spent in different activities by staff at regional, district, and clinic level, payments made to CDDs, and for local services. Survey data on 2005 MDA delivery costs were verified with PNLBG receipts. Drug usage was obtained from district and from PNLBG records. Coverage figures were obtained from district treatment registers and the national annual treatment summary.

Longitudinal surveillance and monitoring data were obtained from records of the Centre de Recherche Medicale et Sanitaire (CERMES) and from the PNLBG register of activities and receipts.

7.5.1. Determination of the economic cost of treatment

The study examines the economic costs of the MDA programme in its first and second years. The economic costs include the full value of the resources used. Where this is not adequately represented by the financial or market cost, an opportunity cost is used (see Table 7.S4). The main cost elements include: the programme specific expenditure; the opportunity cost or value of government contributions related to in-kind costs of using local government staff and vehicles and the value of CDD's time (taken as the daily agricultural labour rate); and the international costs of programme co-ordination, reporting and technical support.

Programme costs include directly incurred capital costs; recurrent costs; and variable costs. Capital costs incurred by the programme included central level purchase of Information Technology (IT), medical and laboratory equipment and other electrical and mechanical goods and furniture used to equip the PNLBG office including the purchase of four 4×4 vehicles for PNLBG (Table 7.S1). Capital costs were annualised over their useful lives (Table

7.S2) using a discount rate of 3%. This represents the annual cost of owning and operating an asset over its lifespan.

Programme recurrent costs including staff costs, office and vehicle running costs, and programme variable costs were collected from the programme records, accounts and receipts. These costs were apportioned in relation to the time spent by programme staff on MDA activities and the proportion of that time allocated to study areas.

Variable costs related to perdiems, materials and services incurred in relation to the programme activities. Centralised activities (e.g. organisation and provision of national training for all district technicians, planning and organisation) and regional activities (e.g. MDA launch) were equally apportioned in relation to the number of districts in the MDA and share of the four study districts. Location specific activity costs such as supervision, mapping, central delivery of drugs to districts were allocated on the basis of costs incurred in the study districts.

Sentinel monitoring informs the national treatment strategy. The costs of sentinel site monitoring were apportioned to the study districts on the basis of study area treatments relative to national treatments.

Government staff costs were based on salary costs collected through questionnaire and the Government salary grid. District and sub district vehicle usage was calculated from questionnaire returns and costed using hire rates. These values are estimated to reflect the opportunity cost of using the resources for the MDA rather than for an alternative activity.

Costs were collated and classified by three levels of organisation (national, regional & district, or community), type of activity (training, support & supervision, baseline & monitoring, reporting, evaluation, advocacy, mobilisation & IEC) and cost type (fuel, transport, materials, services, drugs, per diems, temporary contracts and office related recurrent costs).

Prices are in constant 2005 terms (Table 7.S4). Foreign exchange was converted at the fixed rate of CFA 655/Euro and $1.244/Euro (http://www.federalreserve.gov/release/January 2 2009). Discounted economic analysis was undertaken using discount rate of 3% in line with World Bank rates [13]. The cost of a treatment includes both albendazole and praziquantel.

7.5.2. School based and community delivery system cost calculation

Community and school based delivery was and is practised nationally. The costs incurred by the two systems were equally attributed at national, regional and district level. It is at sub district level that the systems differ in the organisation and implementation of the delivery activities. The school and sub district delivery services used a partial analysis which took account of these cost components only.

The cost of delivery using a CDD and of using a teacher was calculated. These costs included per diems and travel allowances for CDD and head teacher training; allowances for delivery (applicable only for CDD), health clinic staff costs for CDD selection (per diems and fuel) and supervision (fuel only). The training of one or more teachers and their supervision in schools was undertaken by the school head, no financial cost was incurred. Joint activity costs of the district health and education inspectorate (training, drug repacking, drug delivery to sub districts and schools and supervision) would be incurred despite the system. These have not been included in the partial analysis but an allowance has been estimated to allow comparability with other MDA programmes.

7.5.3. Cost effectiveness analysis

The effectiveness of treatment was calculated as the difference between the population with schistosomiasis infection at baseline and follow-up survey. The prevalence rates used are from a longitudinal health impact study (Nadine Seward (2007) Niger Three Years Data Analysis, SCI internal report (unpublished)).

To assess the effectiveness of the programme's direct and direct and indirect treatment effects an assessment of the impact in the treated population and in the targeted population was made. Treatment costs were calculated as the number of treatments in each year multiplied by the full economic cost in 2004/5 and in 2005/6.

Eight schools and four communities located in areas highly endemic for schistosomiasis took part in a longitudinal health impact study. The study used baseline and longitudinal follow-up surveys one year post treatment to monitor: parasitological indicators (prevalence and intensity of helminth disease examining stool and urine samples following standard procedures using kato katz and filtration methods [14]); morbidity indicators (anaemia and

associated pathology of schistosomiasis, assessed by ultrasound examination following standard protocols developed by WHO) and general indicators of height and weight. The baseline survey enrolled 1659 children from 8 different schools in 3 regions prior to the first MDA campaigns of 2004 and 2005. The number of children enrolled from each school ranged from 179 to 299; with almost equal numbers of children in age groups of 7, 8 & 11 years old. Of those recruited 1193 (72%) were followed-up successfully at year 1 and year 2 surveys. Adults and adolescents were monitored in 4 sites in a single region. A total of 484 adolescents and adults were recruited at baseline. Of these, 143 (30%) were followed-up successfully at both year 1 and year 2 surveys. The sample size was estimated using the same criteria as described in [15].

The surveyed sites mirror the MDA treatment and represent MDA performance in targeted populations taking into account the treated and untreated participants in proportion to the MDA coverage. Any indirect effect of reduced infection in untreated pupils resulting from changes in the force of infection is reflected in the intensity of infection [16] which is related to prevalence ([17] provides more detail). To assess the wider impacts on the community, untreated first year students were monitored in the schools. Adults and adolescents were monitored at four sites.

7.6. Results

7.6.1. Total economic costs of treatment

The total economic cost of the programme including programme specific expenditure, national and local government costs and international technical support and programme co-ordination in four study districts, over two years, was US$ 456,718 (Table 7.2); an economic cost per treatment of $0.58. Excluding international costs, the programme and government expenditure was $0.54 per treatment. The programme expenditure per treatment was $0.44. The average drugs cost was $0.28 per treatment. The numbers treated in these two years totalled 818,562 (781,883, discounted at 3%).

Table 7.2: Discounted economic cost of the MDA programme for April 2004 to March 2006 in 4 districts (2005 prices)

Cost Category	National	Regional /District	School, clinic & community	International TC & drugs	Total	Cost Distribution
Programme expenditure						
Capital	10,226				10,226	2%
Recurrent	21,154				21,154	5%
Variable	35,532	17,667	35,261		88,460	19%
Drug cost				222,385	222,385	49%
Total Programme	66,912	17,667	35,261	222,385	342,226	
Programme cost	66,912	17,667	35,261	222,385	342,226	75%
Government cost	3,585	10,721	67,559		81,865	18%
International tech. support				32,627	32,627	7%
Total Economic Cost	70,497	28,388	102,820	255,013	456,718	100%

The distribution of costs between the programme, the government and international support are shown in Table 7.2. Drugs accounted for 49% of the total economic cost (65% of programme expenditure), variable costs accounted for 19% of the economic cost (26% of programme expenditure). Overall there was little difference in the total economic cost of the programme in the four districts between the first and second years. However the total economic cost per treatment in the first year was $0.68 and in the second year was $0.51. Cost differences are shown in Table 7.3 and discussed below

Table 7.3: Annual economic cost of the MDA programme in four districts (2005 prices)

Costs	% distribution*
Capital Costs	5%
Recurrent Costs	
Salary	38%
Vehicle & office fuel	10%
Office & other	2%
Communications	1%
Variable Costs	
Perdiems	26%
Transport	4%
Fuel	5%
Material & services	9%
Total	100%

*Percentage based on discounted cost for the 2 years, $201,705 excluding drugs and international costs.

Excluding the MDA drug costs, the economic cost of the programme in the four districts in the second year was 29% less costly than the first year and treated 25% more people. Higher costs in the first year of the programme are seen in programme costs and international support. Three factors contribute to this. The cost of the initial start up activities incurred in the first year only. The activities involved advocacy, development of IEC materials, prevalence surveys and data collection for planning and the establishment of monitoring and evaluation (M&E) activities, in particular the longitudinal monitoring sites (illustrated in figures 7.2 and 7.3), and repair and maintenance of the national office. In the second year the programme was scaled up. This reduced the apportioned share of recurrent and capital programme costs and international costs allocated to the study area. In 2004/05 22 districts were treated and in 2005/06 40 districts were treated. Within the study area the population treated in the second year which was 25% more than those treated in the first year

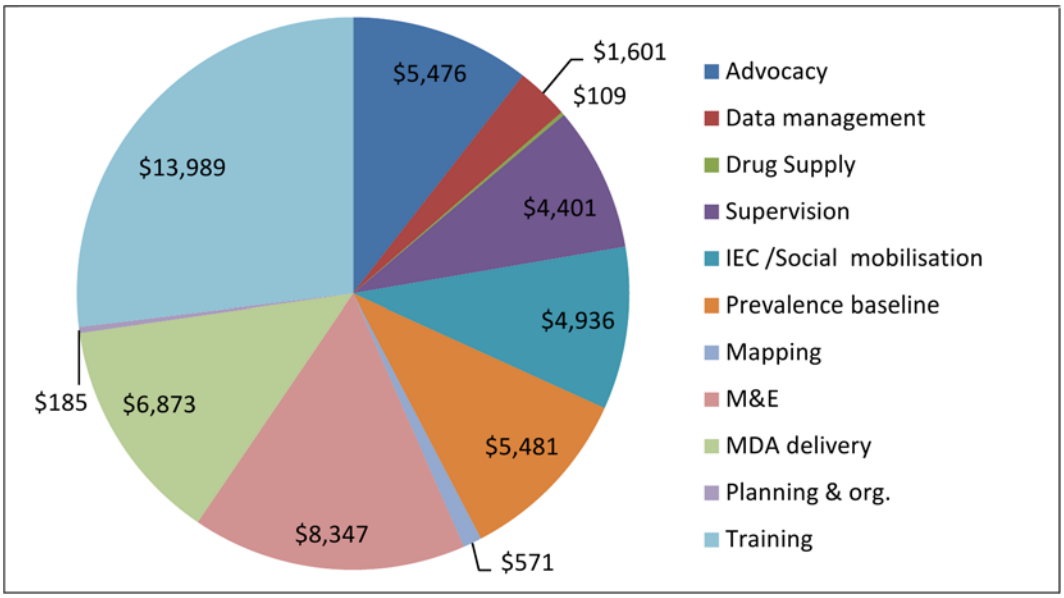

Figure 7.2: 2004/05 Variable costs by activity in 4 districts (2005 prices). Total variable cost was $51,970 in the 4 districts. This includes start up costs involving advocacy, the prevalence baseline, development of IEC materials and establishing monitoring sites. At sub district level, planning and organisation is undertaken at the same time as training

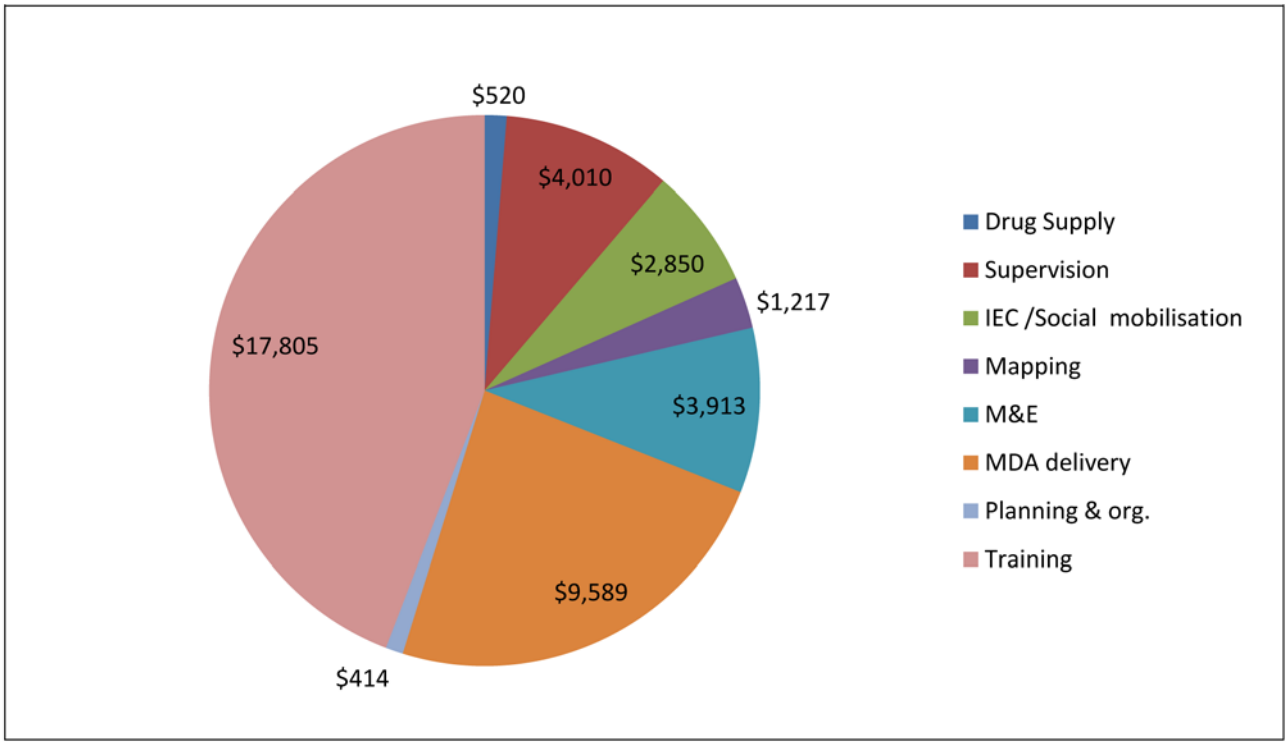

Figure 7.3. 2005/06 Variable costs by activity in 4 districts (2005 prices). Total variable cost was $40,318 in the 4 districts. At sub district level, planning and organisation is undertaken at the same time as training. Compared with the previous year, 25% more people were treated.

The distribution of variable expenditure (excluding drugs) by activity in the study area is presented in Figures 7.2 and 7.3. These show the relatively large proportion of expenditure on training and on MDA delivery. It also highlights activities mainly undertaken at establishment. Total programme variable costs in 2004/05 were $ 51,970 and in 2005/06 were $ 40,318, 22% less than those in the first year.

M&E costs include costs of process monitoring in 2004/5, annual district and regional evaluations and programme health impact monitoring undertaken through the National sentinel sites. These costs amounted to an average of 13% of variable costs over the 2 years. Table 7.4 presents the average allocation of cost by category (capital, recurrent and variable) and type of input. Labour related costs (salary plus per diems) and vehicle and fuel costs account for 64% and 19% of all costs excluding drugs

Table 7.4: Programme and government MDA costs (2004/06) allocated by cost category

Costs	% distribution*
Capital Costs	5%
Recurrent Costs	
Salary	38%
Vehicle & office fuel	10%
Office & other	2%
Communications	1%
Variable Costs	
Perdiems	26%
Transport	4%
Fuel	5%
Material & services	9%
Total	100%

*Percentage based on discounted cost for the 2 years, $201,705 excluding drugs and international costs.

Sensitivity analysis was undertaken on major cost items. A 10% increase in the cost of drugs would result in a 4.9% increase in the total economic cost of treatment ($456,718), and a 6.5% increase in the current programme cost ($342,226). A 10% increase in perdiems and allowances would result in a 1.1% increase in the total economic cost of treatment, or a 1.5% increase in the programme cost, a 4.2% increase in the programme cost excluding drug costs. A 10% increase in wages and salaries would result in a 1.5% increase in the economic cost of treatment. It would impact most on the government sector and distributer opportunity costs increasing costs by 7.7%. The increase on the programme cost would be 0.2%. The sensitivity of total economic cost to a saving in teacher training costs was explored. This assumed community distributers would undertake the school treatments for the same fixed allowance. Savings in teacher training allowances are assumed, but not the economic cost of their time which would still be required to support distributers in school based treatment. Any savings in teacher time would be offset by the increased opportunity cost of time for community distributers. The impact of the net saving on the total economic cost would be 2.9%. This is equivalent to a saving of 4.1% in the programme cost. This provides an approximate scale of magnitude within which to assess comparative costs of sub district delivery systems below.

7.6.2. Cost of community based and school based delivery systems

Sub district costs (i.e. clinic, school and community costs) account for the largest portion of the economic cost by administrative level. This is 23% of the total economic cost (based on Table 7.2); so, it is important to understand the allocation and usage.

Sub district variable programme costs include head teacher and CDD per diems for training and CDD payments for distribution. Sub district government costs include the opportunity cost for the use of motorbikes (11%) and labour (89%). The opportunity cost of labour is principally accounted for by the time of the teacher and head teachers (61%), of the clinic staff in supervision (20%) and CDD time for training and distribution (19%).

Table 7.5 presents the characteristics and costs of sub district delivery. The economic cost per school based treatment and per CDD treatment delivered was $0.36 (range $0.26–$0.55) and $0.06 (range $0.04–$0.07) respectively. The programme cost per school based treatment and per CDD treatment delivered was $0.09 (range $0.07–$0.15) and $0.03 (range from $0.03–0.04) respectively.

The full economic delivery cost of school based treatment in 2005/06 was $0.76, and community treatment was $0.46. If only programme costs are included this figures are $0.47 and $0.41 respectively.

The difference in costs is in part explained by the fact that a CDD delivers 5.8 treatments for every one delivered in school. On average each CDD delivered 407 treatments while each school delivered 70.

Table 7.5: Characteristics and cost of community and school based delivery in 4 districts 2005/06

District	GAYA	KOLLO	TERA	TILLABERI
Characteristics				
No. senior clinic nurses (1 per clinic)	17	16	19	18
No. community drug distributers (CDD)	206	156	300	291
No. schools in campaign	267	324	275	198
Teacher/CDD ratio	1.30	2.08	0.92	0.68
Population Targeted & Treated				
Targeted village population*	103,064	78,084	150,108	145,290
Targeted school related population*	26,872	35,207	32,767	23,266
Treatments by CDDs	75,982	55,820	152,710	103,825
Treatments by teachers	25,121	19,715	12,406	17,245
Treatments administered/CDD	369	358	509	357
Treatments administered/teacher	94	61	45	87
Coverage in villages %	74%	71%	102%	71%
Coverage in schools %	93%	56%	38%	74%
Treated adults	46,653	37,402	69,801	58,895
Treated children	54,450	38,133	95,315	53,320
Overall coverage	78%	67%	90%	72%
Sub District Financial Costs of Treatment				
Teacher cost/treatment $	0.07	0.11	0.15	0.08
CD cost/treatment $	0.04	0.04	0.03	0.04
Sub District Economic Costs of Treatment				
Teacher cost/treatment $	0.26	0.41	0.55	0.28
CD cost/treatment $	0.07	0.07	0.05	0.06

*Targeted populations at school and in the village include both adults and children.
Source: 2005 Survey data, unpublished programme planning data & treatment data 2005/6 campaign.

7.6.3. Cost effectiveness of treatment

Over the 2 treatment cycles 530,300 treatments were provided to an estimated 317,549 adults and 288,262 treatments were provided to 241,218 children in the study areas in the regions of Dosso and Tilaberi. Coverage in the target population in Gaya, Dosso was 78% in both years, and was 69% and 71% in the three districts monitored in Tilaberi.

Two estimates of the cost of treatment per case of infection averted (Table 7.6) are presented. One includes only the direct impacts of treatment and the other includes the direct and indirect impacts of treatment. They provide minimum and maximum limits of the true value. This is discussed further in the next section

Table 7.6: Cost per infection of schistosomiasis averted for children and adults in four districts of Niger

Region/Age	No. Treatments	No. People Treated	No. Targeted	Base Prevalence*	Follow up Prevalence*	Infection Averted (Targeted)	Infection Averted (Treated)	Treatment cost $**	$/Infection Averted (Treated)	$/Infection Averted in (Targeted)	% Difference
Tilaberi –children	227,268	186,768	270,678	93.33%	33.57%	111,613	161,757	122,792	1.10	0.76	45%
Dosso –children	60,994	54,450	69,808	72.37%	19.30%	28,897	37,047	32,219	1.11	0.87	28%
Study area: All children	288,262	241,218	340,486	140,509	198,804	155,011	1.10	0.78	42%		
Adults 2004^	317,549	317,549	446,180	34.12%	18.43%	49,823	70,006	215,933	4.33	3.08	41%
Adults 2004 & 2005^	530,300	317,549	446,180	34.12%	18.43%	49,823	70,006	324,436	6.51	4.63	41%

*Prevalence rates, SCI internal reports (unpublished). Base and follow up figures are significantly different at 95%CI (Table S3).
**Based on full economic costs of $0.68 (2004) and $0.51 (2005)/treatment.
^Prevalence relates to baseline and follow up sample for year 1 in Tahoua region, no adults were monitored in the study area. Drop-out rate at follow up year 2 were high and sample composition differed from baseline.

Including only the direct impacts on the treated population the average cost per infection averted in treated children in the 4 districts over the two years was $1.10. Of the 317,549 adults treated in a single round the cost per infection averted was $4.4 and over two rounds it is estimated to be $6.5. The overall cost per infection averted in the treated population of children and adults is calculated as $2.5.

If indirect treatment effects are included the average cost per infection averted in targeted (treated and untreated) children in the 4 districts over the two years was $0.78. Of the 446,180

adults targeted in a single round the cost per infection averted was $3.08 and over two rounds it is estimated to be $4.6. The overall cost per infection averted in the targeted population of children and adults is calculated as $1.78.

The higher cost of infection averted in adults reflects the lower base prevalence rate. The longitudinal adult cohort followed up over the 2 year period suffered high drop-out rates and its composition was significant different at the 0.05 significance level. Males in particular those who were infected with *S. haematobium* infection were more difficult to retain at follow-up. The resulting cohort of 116 adults had a lower proportion of males, and had a lower base rate of infection (24.1%, (95% CI:16.35–31.93)) as compared with the original baseline sample (39.62% (95%CI:35.23–44.01)). To avoid this issue the results for the sample monitored at the first year follow up are used and it is conservatively assumed that the prevalence in the second follow up did not change.

7.7. Discussion

The cost per treatment and prevalence figures relate to the study sample of four districts located in the Niger River Valley. This was and is an area of high disease prevalence and high population density relative to other parts of the country. The costs per person treated may be higher in lower density and more remote areas. Likewise the cost per infection averted will be greater in sub populations with lower changes in prevalence.

The cost study relied on the survey work for details of district and sub district resource use. As the survey was undertaken almost a year after the MDA, it may have been affected by recall bias. A further limitation of the study is the delay in final analysis. This limited follow-up work; the recent MDA's confuse recall and some key people have changed positions and locations. However, the issues raised by the study analysis are still relevant and worthy of further investigation.

One of the strengths of the study is the availability and use of MDA health impact monitoring results to assess programme effectiveness. Cost effectiveness studies are often obliged to use trials data concerned with the efficacy of treatment [3] rather than programme effectiveness as monitored in Niger. This potentially allows us to capture direct and indirect treatment effects as identified by Miguel and Kremer [18] and French et al [16]. Both identify direct and indirect effects of treatment in terms of the reduced transmission of *Schistosoma*

mansoni in children in the community including children not treated. The direct and indirect impact quantified here represents a best case or maximum impact. Further work based on intensity and force of infection based on the work of French et al [16] is required to refine and triangulate the estimate. Estimating only the direct effects of treatment in the treated population provides a conservative estimate of infection averted. Due to the definition of prevalence used in the study and the data available, the prevalence estimate in the treated population is under estimated (and consequently cost per treatment is overestimated). The true value of the infections averted is believed to be between these two estimates. There is a 40–42% difference in the cost per infection averted between the "best" and worst case scenarios. However the magnitude of difference underlines the importance of refining the method and developing more robust estimates.

The most effective means of delivering helminth treatment to school age children has been debated in various papers. The Partnership for Child Development (PCD) [6] provided evidence from Ghana and Tanzania on the cost of large scale treatment in schools and the potential savings in using the existing school infrastructure for treatment. For many recipients, access to the more numerous schools is more convenient than attending more distant health facilities [19]. However, where school enrolment is low and particular groups (for example girls or the poorest children) are under-represented, there is a need for additional methods of reaching target populations [7]. Studies in Tanzania [20] and Uganda [21] have examined the effectiveness of Community Directed Treatment (ComDT) and school based treatment in terms of coverage for enrolled and non enrolled children. In Tanzania coverage in both systems was similar, whilst in Uganda coverage rates under ComDT was higher; the associated costs are not discussed.

The evidence on the cost effectiveness of three recent large scale helminth MDA studies in Sub-Saharan Africa is summarised in Table 7.7. This presents the characteristics: treatment strategies, distribution methods, coverage levels, activities costed, study duration and the number of treatments rounds provided. Each of these affects the cost and technical effectiveness of the programme.

Table 7.7. Comparison of MDA costs of three vertical helminth control programmes in Sub Saharan Africa

Background Parameters	Note	B. Faso	Uganda	Niger
Strategy	a	A	B	B
School net enrolment 2005	b	40%	n/a	42%
No. districts in costing paper		ALL	6	4
Treatments in study area & period		3,322,564	432,746	818,562
Study period (years)		2	3	2
Activities included in cost	c	1	1+	1,2,3,4,
National coverage	d	91%	79%	66%,78%
PPN treated in communities: schools		1.5:1	0.6:1	5.2:1
PPN targeted in communities: schools	e	1.64:1	0.85:1	2.7:1
Costs included	f	2, 3a	2,3	1,2,3
Discounted analysis employed		No	Yes	Yes
Programme costs/treatment				
Economic	g	n/a	n/a	0.54 (0.58)
Financial or programme cost	g	0.32	n/a	0.44 (0.48)
Drug cost	h	0.22	0.22	0.28
Economic cost/treatment by system				
School based	g	n/a	0.54	0.74 (0.76)
Community based	g	n/a	n/a	0.44 (0.46)
Financial cost/treatment by system				
School based	g	0.31	0.39	0.45 (0.47)
Community based		0.33	n/a	0.39 (0.41)
Sub district programme delivery cost treatment				
Cost/person school based delivery	i	(0.08)	0.16	(0.09) 0.11
Cost/person CDD delivery	i	(0.11)	n/a	(0.03) 0.05

Notes.
a A. All SAC 1 treatment over 2 years, B All SAC in target areas & key adults C SAC 2 or more treatments.
b Rates as reported by UN ISCED level. Uganda rates are considered to be more the SSA average of 68%.
c 1. MDA 2. mapping 3. M&E 4. Prevalence surveys 5. Screening.
d B. Faso coverage over 2 years (2004–2005), Uganda: coverage in pilot phase (2003), Niger: coverage in pilot phase (4-2004/4-2005) and second phase (4-2005/4-2006).
e Based on first year results in Niger and Uganda.
f 1. International support costs, 2. Programme expenditure and costs, 3. Government contribution a) cash & b) recurrent in kind costs (e.g. staff salaries and vehicle usage).
g see activities included () including international cost.
h Drug usage estimated in Uganda. In Niger usage is based on district registers and is not stated in B Faso.
i district costs and () sub district costs. Costs exclude drugs, Uganda delivery cost is reduced by 5% to allow for central overheads.
n/a not available n/r not relevant.
Sources: [4],[5],[16].

Prevalence and mapping data facilitate treatment prioritisation of endemic areas. This reduces the numbers treated, easing pressure on constrained budgets, but allows the option, to treat targeted at risk adults. Niger and Uganda used a targeted approach. Burkino Faso undertook a blanket approach and treated all school children in the first treatment.

Burkina Faso has the lowest financial cost per treatment but excludes start up, mapping and M&E costs included in the studies (see Table 7.7); it also has the highest coverage. Coverage is a key factor in determining costs per treatment; in particular capital and recurrent costs. Children accounted for all treatments in Burkina Faso and 53% of treatments in the Niger study. Niger's targeted strategy reduced the numbers of children requiring treatment. This eased the budget constraint allowing the targeted treatment of adults, and increased the scale economies of the programme.

Niger and Uganda provide a measure of the effectiveness of treatment. Infections averted are used based on anaemia in Uganda and schistosomiasis in Niger. The use of a technical measure of effectiveness provides the opportunity to assess, both ex-ante and ex-post the potential cost effectiveness of alternative strategies.

The sub-district school based delivery cost per treatment is similar between Niger and Burkina Faso (a difference of 10%). Uganda district school based delivery costs (allowing for central programme costs) are almost 45% greater than Niger's. The reason for this is not clear. It may be that central costs are included in activities other than “programme costs” Sub district community delivery cost per treatment in Niger are significantly lower than Burkina Faso due to the high numbers targeted and treated. The low levels of enrolment, low school numbers targeted and lower coverage rates all add to the relative cost per person of the Niger school based system.

The cost per person treated can be reduced either by increasing national coverage or by an improvement in resource efficiency. Alternative means of school based implementation are available and school based treatment can be delivered by teachers, health workers or CDDs, training may or not be required annually. However the differences in delivery will impact on treatment acceptability [19] and coverage, collaboration and motivation as well as the variable costs.

The distribution of programme costs in Niger, suggest cost savings would have greatest impact in drugs and training. Drugs are a major component of the treatment cost and account

for almost half of the economic cost in the current study, between 27%–46% per district of the economic cost in Uganda and 69% of the financial cost in Burkina Faso. The central procurement (undertaken in 2004/06 by SCI) improved the buyer's market power, described by Fenwick and Thompson [12]. On average 3.1 praziquantel tablets and 1.4 albendazole tablets were consumed per treatment in the current study. Using an estimate of actual against planned praziquantel usage (3.5 tablets/adult and 2.5 tablets/child), gave an average difference of 6% with a range of −4% to 23% across the four districts. The average rate is considerably more than the wastage rate of 1% assumed in [5]. This range shows a considerable discrepancy between districts and emphasises the importance of robust drug monitoring and reporting system.

Targeted treatment of at risk adults in high endemic areas is used in Niger and Uganda in line with WHO guidelines. As the cost per infection averted in adults was 3.5 greater than for a child, it is important to understand the economic value of adult treatment. One approach is to assess the direct benefits in terms of impact on adult productivity and the value of this productivity. USAID Famine Early Warning System Network (FEWS-NET): Niger Livelihoods Profiles, provide a useful description of livelihood profiles in these areas. Two studies, with agricultural production comparable to that in the Niger study, report the impact of schistosomiasis on agricultural labour productivity [22], [23]. The impact of schistosomiasis treatment on family labour in paddy rice growing systems in Mali [22] found that health is improved due to schistosomiasis treatment. As a result the time available for farm work by family workers increased by 69 days/ha. Much of this time was invested in the cultivation of additional non irrigated land, (0.47 ha) (if it is assumed a family has 7-10 members, the average improvement / person would be 10-7 days.). The days of family farm labour lost due to schistosomiasis and other parasitic and non parasitic infections was assessed in rain fed farm systems in Benue State, Nigeria [23]. In these systems 46% of time lost due to illness was related to schistosomiasis, an average loss of 18.7 working days per adult. The cost per adult of infection averted in Niger in the first round is estimated here as $4.3 (Table 6) equivalent to 3 days of labour (based on the agricultural day rate ($1.4) in 2005, a year of famine) or 2.3 days (based on rate of $1.9 in a normal year). This indicates the potential economic net gain from adult treatment. The gain could be greater depending on adult rates of re-infection and consequent treatment need.

7.8. Conclusion

The cost of treatment per person is driven by the scale of treatment. The strategy, in Niger, to include targeted adults as well as school age children has increased the treatment numbers and reduced the cost per person treated and increased effectiveness. A conservative estimate of cost effectiveness over 2 years for the treated population is estimated to be $1.1 per infection averted for children and $6.5 for adults.

This study used a targeted treatment strategy; 53% of treatments were to children, but only 16% of the population treated received school based treatment. Under these conditions community based treatment was more cost effective than school based treatment. In Burkina Faso, only school age children were treated; 40% of these received school based treatment); the school based system was more cost effective per treatment. However, the school and community based distribution systems serve overlapping groups in the population; and was designed to facilitate access to treatment for different groups and support a coverage rate of 75% or more in target populations. Any improvement in either system must be the result of improved resource use or increased coverage at the district and programme level if the change is not to impact on the effectiveness of the other system.

In designing cost effective and sustainable programmes factors relating to: the treatment strategy, the demographic mix of the population served, system acceptability to stakeholders and the coverage rate need to be taken into account along with logistic issues such as health staff availability. Economic and financial assessment of alternative implementation plans should be undertaken for the project or programme design. This would support decision makers and programme managers, provide financial evidence in planning discussions and negotiations and potentially reduce the need for programme changes to improve cost effectiveness.

7.9. Acknowledgements

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7.11. Supporting information

Table 7.S1 Summary of principal programme unit costs * Average dose 1.4 tablets Albendazole, 3.1 tablets Praziquantel includes adult & child consumption and wastage

Category	Input	Units	Unit Cost $	
			Minimum	Maximum
Capital Items	Office building	Annualised cost	11,342	
	Project vehicle	Purchase cost	24,669	48,251
	Computer	Purchase cost	1,500	
	Photocopier	Purchase cost	5,104	
Salaries				
	National Co-ordinator	per month	417	
	Central Technical Staff	per month	125	330
	Central Administrative staff	per month	125	220
	Driver	per month	110	
		District & Regional Health		
	District & Regional Staff		216	340
	Clinic Head Nurse	per month	136	216
	Certified Nurse	per month	93	
	Community Health Worker	per month	38	66
	Distributer	per month	38	95
	District & Regional Education			
	Inspectorate Staff	per month	244	309
	Teachers - civil servant	per month	171	227
	Teacher -contracted	per month	75	100
Allowances	Central Technical Staff	per day	19	28
	District Staff	per day	19	
	Training participant	per session	5	
	Community distributer	per local distribution	5	
	Driver	per day	5	
Consumables	Phone cards	per card	1.9	
	IEC poster	per unit	0.1	
	Technical sheets	per unit	0.1	
	Treatment register	per unit	0.2	
	Dose poles	per unit	2.8	
	Radio broadcast	per broadcast	18.9	
	Albendazole	per dose *	0.04	
	Praziquantel	per dose *	0.24	
	Hire rate / 4x4 (in district)	per day	70.9	
	Hire rate / motor bike	per day	9.5	
	Fuel	per litre	1.1	

Table 7.S2: Life of Capital assets

Asset Category	Years of life
Electrical and mechanical goods	5 and 10
Furniture	10
IT equipment	5
Medical equipment short life	5
Medical equipment medium life	10
Phone	10
Vehicles	5

Table 7.S3: Mean prevalence and confidence limits of base line and follow up surveys in study areas. Table S3 provides further detail of the mean and 95% confidence intervals used to estimate the cases averted in estimating the costs per case averted. In Gaya, Dosso region the prevalence rates are higher in the second follow up compared with the first. The reason is not known, but may relate to difference in coverage in the surveyed school. Coverage is available at district level, and sub district data is collated at district level, but is difficult to obtain retrospectively. The followed up for children over the two years was high (81%).

Region/year	95% Confidence Interval		
Tilaberi (7-15 yrs)	Mean	Lower	Upper
Base line	93.33%	90.95%	95.72%
Follow Up 1	45.48%	40.71%	50.24%
Follow Up 2	33.57%	29.06%	38.09%
Dosso (7-15 yrs)			
Base line	72.37%	66.56%	78.17%
Follow Up 1	13.60%	9.15%	18.05%
Follow Up 2	19.30%	14.18%	24.42%
Adults			
Base line	34.12 %	28.30%	39.94%
Follow Up 1	18.43 %	13.67%	23.19%

Table 7.S4: Glossary of terms

Term	Meaning
Annualise	This is the cost per year of owning and operating an asset over its entire lifespan, sometimes called the equivalent annual cost
Constant prices	A value from which the overall effect of general price inflation has been removed, also known as real prices.
Discounting	A mechanism by which values which occur in future years are weighted (set by the discount rate) to ensure that the time value of money is taken into account.
Discount rate	The economic opportunity cost of capital or the economic rate of return on alternative marginal projects or investments.
Financial prices	These are the actual prices at which inputs are bought and outputs sold and are used in financial analysis. In economic analysis, where prices are distorted due to market or government failure, it is necessary to impute the price that reflects the real economic value of an input or output. The opportunity cost may be used to reflect this value.
Net primary school enrolment (NER)	Enrolment of the official age group for a given level of education expressed as a percentage of the corresponding population.
Opportunity cost:	The benefit or value that could have been gained from an alternative use of the same resource.
Present value	Sum of one or more annual discounted values

8. Discussion and conclusion

The most important findings of this PhD thesis pertaining to the epidemiology and control of schistosomiasis in sub-Saharan Africa can be summarized as follows:

- We found considerable prevalence and morbidity due to schistosomiasis in infants and preschool-aged children in selected villages of Niger. In one setting, these young children harboured *S. haematobium* and *S. mansoni* and, a non negligible proportion of them, were co-infected.
- Mother's behaviour (i.e. taking young children to open freshwater sites where they are washed and bathed) is a key risk factor for children to become infected at an early age.
- Praziquantel is safe and efficacious in *S. haematobium* infection inducing high cure and egg reduction rates in school-aged children. Two closely spaced doses of 40 mg/kg of praziquantel (given at a 3-week interval) showed good tolerance and efficacy against *S. haematobium.*
- In preschool-aged children, praziquantel syrup is well tolerated and efficacious against *S. haematobium* at the standard dose of 40 mg/kg.
- Treatment of preschool-aged children with praziquantel syrup was shown to be operationally feasible.
- Against *S. mansoni* praziquantel showed moderate-to-low cure and egg reduction rates at the standard dose of 40 mg/kg. Two closely spaced doses of 40 mg/kg of praziquantel to school-aged children and treatment of preschool-aged children showed reasonable cure and egg reduction rates.
- The average overall cost per person treated for schistosomiasis and soil-transmitted helminthiasis, including the cost of the drugs, is US$ 0.58.

8.1. Challenges for sustainable schistosomiasis control in sub-Saharan Africa

Sustainability of control interventions is essential to reach the goal of long-term morbidity reduction and eventually elimination of schistosomiasis, a disease that is intimately linked to poverty (WHO, 2002; King, 2010). Social and economic development, and hence improving the quality of life and wellbeing, is the ultimate solution to schistosomiasis control

as we have witnessed in Japan, St. Lucia and other Caribbean Islands, People's Republic in China, Korea and partially in Egypt (Webbe, 1987; Tanaka and Tsuji, 1997; Utzinger et al., 2005). Increasing the education level by sending children to school as far as possible are key factors in promoting early behavioural changes, which in turn will improve health (Miguel and Kremer, 2004). Provision of safe water and improved sanitation facilities and their use by the population will support changes in behaviour towards water contact patterns and reduce environmental contamination (Jordan and Unrau, 1978; Jordan et al., 1982; Utzinger et al., 2003). However since independence, progress in several African countries in theses domains remained slow (http://hdr.undp.org/en/reports/global/hdr2010) because of lack of resources or merely insufficient political commitment (Zhang et al., 2011). Meanwhile, PCT is the only proved safe and low-cost strategy to have a rapid impact on schistosomiasis (Molyneux et al., 2005; Fenwick et al., 2009). PCT strategy involving integrated control of several diseases is an excellent mean to move forward the control of schistosomiasis (Molyneux et al., 2005; Hotez et al., 2006; Utzinger and de Savigny, 2006; Hotez, 2009). By taking advantage of a single drug delivery system and the same distribution channel (e.g. community drug distributors or school teachers), MDA cost are considerably reduced. This led to an increase of the countries implementing PCT in sub-Saharan Africa with international support (Savioli et al., 2009). Free drug donation programmes and involvement of big funding agencies (USAID, DFID, BMGF) gave a strong boost to the control supported by a continuous strong advocacy campaign (Hotez et al., 2007; Linehan et al., 2011; Zoerhoff et al., 2011).

New reports suggest that the progress made in recent years may slow down. Among other reasons, there might be drug shortages. For example, in 2010, Hotez and colleagues have alerted the scientific community that there might be PZQ tablet shortage, should treatment target put forth by WHA be met (Hotez et al., 2010). Indeed, the PZQ need would be 1 billion tablets per year in order to treat 400 million individuals through PCT. In 2011, this PZQ treatment shortage has become a reality (http://www.who.int/neglected_diseases/schistosomiasis_WHO_calls_for_action/en/index.html), resulting in MDA campaigns postponed on the ground because of late delivery of drugs. This shortage occurs while highly populated countries where schistosomiasis remain highly endemic (e.g. Nigeria and Ethiopia) have not yet started to implement nationwide control. The PZQ production is not following the need and this will become a major stumbling block to the further scaling-up of the control of schistosomiasis. Hence, there is an urgent need to increase

the production to fulfil the treatment gap created by the increasing number of countries implementing control (Reich, 1998).

Another limiting factor is the strong dependence of these control programmes from external donors. Only few African countries make major investments in the control of NTDs. However, international donor support usually is just for a couple of years, so increasing the part of health budget to NTD control is important (Zhang et al., 2011). Our study has shown that the cost per person treated is US$ 0.58 including the cost of the drug. This cost was US$ 0.54 in Uganda (Brooker et al., 2008) and much lower in a study in Burkina Faso, where it is only US$ 0.32 (Gabrielli et al., 2006). With the current advocacy towards drug companies, if more PZQ is eventually produced and donated, this cost will be just reduced to operational costs that might be more readily handled by the countries if there is sufficient political will.

8.2. Maintaining the reduction of morbidity achieved

Several years of PCT implementation have led to a considerable reduction of schistosomiasis endemicity in many countries to prevalence level below a pre-set 10% threshold where MDA is not required any longer according to current WHO guidelines (Kabatereine et al., 2007; Toure et al., 2008). Nevertheless, some hot spots with continued high transmission remain. In such circumstances, the question arises whether countries should continue or stop their MDA campaigns. Stopping MDA is risky, particularly in the absence of sound surveillance systems and where access to clean water and improved sanitations remain elusive. Health systems are often not ready to manage the necessary minimum essential activities at the district level, such as diagnosis, epidemiological surveys, decision to treat, and other related issues (Utzinger et al., 2009). Experience with interruption of control activities has shown rapid resurgence, when MDA is stopped without any activities and maintenance, and hence morbidity quickly comes back to pre-intervention levels (Daffalla and Fenwick, 1982; Wagatsuma et al., 1999; Scrimgeour et al., 2001; Gray et al., 2011). Resurgence of schistosomiasis should by all means be avoided. Hence, before stopping MDA, control should be decentralized at district and drug widely available, so that district management teams will be ready to take the lead for further activities, such as identification and mapping of remaining hot spots that warrant PCT, integration of diagnostic and treatment in routine activities of the health facilities, and establishment of community-based surveillance. There is a need of continued capacity building and development of operational tools and guidelines at

all possible levels. Meanwhile, since a schistosomiasis vaccine is still not available and no proven strategy for long-term maintenance of PCT programmes is in place, it is currently recommended to continue MDA, and hence to keep taking the PZQ tablets (Hagan et al., 2004). Cost studies aiming to compare the cost-effectiveness of a continued MDA and an increased mapping with target treatment will be helpful to choose the most economic approach to sustaining control efforts. Another issue that warrants further scientific inquiry is the minimum coverage rate of MDA to have an impact on transmission (King et al., 2006) and how to deal with systematic non-compliance for repeated rounds of MDA (Parker et al., 2008).

8.3. Monitoring the efficacy of PZQ

This thesis also raised the issue of PZQ efficacy, the only drug currently used for morbidity control of schistosomiasis with a huge predictive increase of its use in sub-Saharan Africa in the years to come. Monitoring the efficacy and safety of PZQ is an important issue to ascertain that the drug will remain effective and that the objective of reducing and consolidating the morbidity will be reached (WHO, 2002; Albonico et al., 2004). Generally, PZQ has shown high efficacy against *S. haematobium* at the recommended dose of 40 mg/kg with extremely high ERR and moderate-to-high cure rates (Danso-Appiah et al., 2009). Recently a multicentre trial carried out in Brazil, Mauritania, Tanzania and the Philippines, confirmed the high efficacy of PZQ against *S. mansoni* and *S. japonicum* at the standard dose of 40 mg/kg, and hence it was concluded that it is not necessary to increase the dose to 60 mg/kg (Olliaro et al., 2011). However, in our study, only moderate efficacy was observed against *S. mansoni* even with two closely spaced doses of 40mg/kg given 3 weeks apart. Similar observation have been made in Senegal (Tchuem Tchuente et al., 2001), Côte d'Ivoire, (Raso et al., 2004) and Uganda (Kabatereine et al., 2003). We therefore recommend continued monitoring of PZQ efficacy. More elaborated and standardized study protocols (Danso-Appiah et al., 2009), including drug quality assessment (Botros et al., 2011) are required, as well as a treatment strategy scheme with two rounds of MDA in highly endemic areas or reducing the treatment frequency to once every second year. SCORE is currently investigating different treatment schemes, including treatment holidays, in different countries of sub-Saharan Africa.

8.4. Including preschool-aged children in PCT

Including preschool-aged children in PCT must be considered, since several studies have shown high infection prevalence and morbidity in this age group (Ekpo et al., 2010; Garba et al., 2010; Dabo et al., 2011; Stothard et al., 2011). All people needing PZQ should have access to the drug and no community group should be left out. Thus, including preschool-aged children is justified from public health and equity points of view and will allow reducing the treatment gap which might also have an effect on transmission control (Johansen et al., 2007; Stothard et al., 2011). While MDA have reduced the prevalence of schistosomiasis to less than 10% in school-aged children in several countries implementing PCT, it is not reasonable to keep the preschool-aged children untreated and let them be an important reservoir of transmission in the community. Recent studies not only showed that PZQ is safe and efficacious in preschool-aged children, but also developed and proposed a dose-pole for easy treatment of young children during MDA (Sousa-Figueiredo et al., 2009, 2010; Mutapi et al., 2011). However this dose pole needs to be further validated in other settings. The current PhD thesis showed that PZQ syrup is safe and efficacious. Logistic concerns about the introduction of syrup in MDA come mainly from the management of the volume of drug and, consequently, the cost of transport and storage.

Another issue is the need of paediatric scale to weight preschool-aged children, but this could be solved if the proposed dose-pole is further validated in other settings. Experiences in countries endemic for trachoma where Zithromax® syrup is distributed proved that distribution of syrup during MDA is indeed feasible. Additional studies are underway in Mali, Burkina Faso and Niger and, thus far, no major problems have been raised (Zoerhoff et al., 2011). Zithromax® syrup bottles are considerably larger than the one used for PZQ and contain dry powder, which needs to be mixed with clean water before administration. Storage problems have been observed at country level and in some districts because of the large volume of the syrup. In the case of PZQ syrup, however, the volume is certainly much lower considering the fact that PZQ bottles are smaller than the ones currently used for zithromax®, and also because of the limited target of the syrup, which determine the quantity of drug. Schistosomiasis is focal in endemic communities, while the distribution of trachoma drug is district-wide for all the children. However, before including the syrup in MDA, there is a need to improve the bioavailability of the PZQ syrup. Meanwhile, crushed tablet which have a similar efficacy with syrup can continue to be used.

9. Research needs

This PhD thesis identified a number of research needs, which are offered for consideration. We believe that addressing some of these identified needs will contribute to further enhance and reinforcement of the control of schistosomiasis in sub-Saharan Africa.

- Laboratory and field studies to investigate the low susceptibility of *S. mansoni* to PZQ are necessary. These studies should have robust protocols and focuses on genetic studies of the *S. mansoni* strains as well in vivo and vitro efficacy tests.
- Large-scale studies (at district level) of MDA including administration of PZQ syrup should be undertake to identify all the details of the operations issues that will be raised by the introduction of PZQ syrup in PCT.
- Cost and epidemiologic studies aiming to compare the effectiveness of a continued MDA and an increased mapping with target treatment should be conducted in order to choose the best economic and morbidity control approach to maintain the reduction of morbidity achieved.
- Studies aiming to determine the minimum coverage rate of MDA to have an impact on transmission are important to deal with systematic non compliance for repeated rounds of MDAs.

10. References

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11. Curriculum vitae

1. Identity

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2. Education

- PhD in Epidemiology at the Swiss Tropical and Public Health Institute, Basel, Switzerland (Thesis defence September 2011).
- Master of Science Epidemiology and Biostatistics, University of Bordeaux 2, France, 2004
- Master of Public Health. Institut Régional de Santé Publique de Cotonou (Bénin), Université nationale du Benin, 1999.
- Degree of Doctor in Medicine. Faculté des Sciences de la Santé, Université de Niamey-Niger, 1992.

3. Current Post

- Coordinator of RISEAL-Niger, responsible for SCI implementation and research projects in Niger

4. Work Experience

4.1. Work positions held

- **2007-April 2011**. Coordinator of the Neglected Tropical Diseases Control Programme of Niger
- **2004-2007**: Coordinator of the National control programme for Schistosomiasis and Soil-transmitted Helminths of Niger
- **1993-2004**: Researcher in the Epidemiology Unit of CERMES (Center of Research on Meningitis and Schistosomiasis) of Niamey. WHO, collaborating center for research and control of schistosomiasis.
    - Principal investigator of the phase 2 clinical trial of the anti schistosomiasis vaccine Sh28GST “Bilhvax” in Niger (2000-2001).
    - Principal investigator of phase 2 clinical trial of the conjugate bivalent A/C anti meningococcal vaccine of Aventis in infants (1994-2000)
    - Technical support for evaluation of morbidity due to schistosomiasis near dams (Bagré, 1997, and Ziga dams 1998 in Burkina Faso and Adjarala dam in Benin, 2000.

- **1992-1993**: Deputy to the Director of Téra Health District

4.2. Technical support / Consultancies

- **2001- To date:** Temporary advisor of WHO on Neglected Tropical Diseases Control Programme implementation in Afro area. I provided technical support to countries and participated to technical meetings in the WHO/HQ
  - Temporary advisor for the training workshop for the WHO consultants for the finalization of the countries NTD master plans. Niamey, Niger, 18-23 April 2011.
  - Temporary advisor for the preparation of "Strategic plan for STH Control". Department of Control of Neglected Tropical Diseases (NTD). WHO/HQ, Geneva, Switzerland, Room M405 - 11 & 12 April 2011
  - Temporary advisor for the informal consultation on schistosomiasis control. Geneva, Switzerland, Salle D, 31 March to 1 April 2011.
  - Technical support to Rwanda (22 February-2 March 2011) and Uganda (4-9 March 2011) for the finalization of their Master Plan for the control of Neglected Tropical Diseases.
  - Temporary advisor for the meeting to review results from studies on the treatment of young children for schistosomiasis, WHO/HQ, Geneva, 13-14 September 2010
  - Temporary advisor for the informal working group meeting on urogenital schistosomiasis and HIV transmission, WHO/HQ, Geneva, Switzerland, 1-2 October 2009.
  - Temporary advisor of WHO/AFRO for the regional training workshop on implementation of Preventive Chemotherapy strategy (Ouidah, Benin, February 2008)

Consultant of the Ministry of Education of Niger for the elaboration of the School Health Strategic Plan (2008)

5. Training Courses

- January 2006: Strategic Financial Management for NGOs – Managing for Financial Sustainability (Lusaka, Zambia)
- August 2004: Financial Management for Non-Governmental Organizations training course. Ouagadougou, Burkina Faso.
- September 2004: Organizer and trainer of a regional workshop on the use of ultrasound for the schistosomiasis morbidity assessment (Niamey, Niger).
- September – November 1993: Ultrasonography training for the evaluation of morbidity due to schistosomiasis. Radiology Department at the Children's Hospital in Tunis.
- 1994-2011: Supervision of 10 Medical Degree thesis (University of Niamey, Niger and University of Mali), 3 Master Degree of Public health and Epidemiology (Niger Institute of Public Health) & 1 Imperial College of Science and Technology *PhD* thesis.

6. Publications:

1. **Garba A,** Sani Lamine M, Barkiré N, Djibo A, Sofo B, Gouvras NA, Labbo R, Sebangou H, Webster JP, Fenwick A, Utzinger J. Efficacy and safety of two closely spaced doses of praziquantel against *Schistosoma haematobium* and *S. mansoni* in school-aged children and re-infection patterns in Niger. *Submitted to Acta Tropica*
2. Stothard, J., Sousa-Figueiredo, J.C., Betson, M., Green, H.K., Seto, E.Y., **Garba, A.,** Sacko, M., Mutapi, F., Vaz Nery, S., Amin, M.A., Mutumba-Nakalembe, M., Navaratnam, A., Fenwick, A., Kabatereine, N.B., Gabrielli, A.F., Montresor, A., 2011. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology* (in press).

3. Schur N, Hurlimann E, **Garba A**, Traore´ MS, Ndir O, et al. (2011) Geostatistical model-based estimates of schistosomiasis prevalence among individuals aged ≤20 years in West Africa. *PLoS Negl Trop Dis* 5(6): e1194.
4. Molyneux D, Hallaj Z, Keusch GT, McManus DP, Ngowi H, Cleaveland S, Ramos-Jimenez P, Gotuzzo E, Ka K, Sanchez A, **Garba A**, Carabin H, Bassili A, Chaignat CL, Meslin FX, Abushama HM, Willingham LA, Kioy D. Zoonoses and marginalised infectious diseases of poverty: Where do we stand? *Parasites & Vectors* 2011, 4:106
5. Ibironke OA, Phillips AE, **Garba A,** Lamine SM, Shiff C. Diagnosis of *Schistosoma haematobium* by Detection of Specific DNA Fragments from Filtered Urine Samples. *Am J Trop Med Hyg*. 2011, 84(6):998-1001.
6. Ouldabdallahi M; Ouldbezeid M; **Garba A**; Mbaye A et Konaté L. Parasitoses intestinales et schistosomoses sur la rive droite du Fleuve Sénégal, République islamique de Mauritanie. *Ann. Afr. Med., Vol. 3, N° 4, Sept 2010*, 566-573
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9. Baker MC, Mathieu E, Fleming FM, Deming M, King JD, **Garba A,** Koroma JB, Bockarie M, Kabore A, Sankara DP, Molyneux DH. Mapping, monitoring, and surveillance of neglected tropical diseases: towards a policy framework. *Lancet*. 2010 Jan 16;375 (9710):231 8.
10. **Garba A,** Touré S, Dembelé R, Boisier P, Tohon Z, Bosqué-Oliva E, Koukounari A, Fenwick A. Present and future schistosomiasis control activities with support from the Schistosomiasis Control Initiative in West Africa. *Parasitology*. 2009 Nov; 136 (13):1731-7. Epub 2009 Jul 27.
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12. Sousa-Figueiredo JC, Basáñez MG, Khamis IS, **Garba A,** Rollinson D, Stothard JR. Measuring morbidity associated with urinary schistosomiasis: assessing levels of excreted urine albumin and urinary tract pathologies. *PLoS Negl Trop Dis.* 2009 Oct 6; 3 (10):e526.
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35. **Garba A**, Aboubacar A, Barkire A, Vera C, Sellin B, Chippaux J-P. [Impact of health education campaigns on the control of urinary bilharziasis in Niger]. *Cahiers Santé*, 11 : 35-42, 2001.
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6. Affiliation with associations and membership of scientific committees

- Member of the French Society of Exotic Pathology http: //www.pathexo.fr
- Member of the Royal Society of Tropical Medicine and Hygiene
- Member of the International Network " Schistosomiasis, Environment, and Control " http: //www.riseal.org
- Member of the network Parasitic and Vectorial Diseases (MVP) of the University Agency of French-speaking world http://www.mpv.auf.org
- Member of the Research Network for Schistosomiasis in Africa RNSA http://www.rnsafrica.org
- Member of the WHO/TDR Disease Reference Group on Zoonoses and Marginalized Infectious Diseases of Poverty ZOOM-IN (2009-2010)
- Member of the Lymphatic filariasis elimination African regional programme review group (Since 2009)