The epidemiology, surveillance and control of malaria in Kenyan school children

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Declaration by candidate

I, Caroline Wangui Gitonga, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed. Date.30th May 2013

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Abstract

School-aged children are the age group least protected by malaria interventions such as bed nets, despite being the age group most likely to be infected with malaria parasites. Effective targeting of malaria interventions among this age group is hampered by the lack of detailed data on the epidemiology of malaria.

This thesis aims to describe the epidemiology of malaria among school children in Kenya and explores the usefulness of school-based approaches in malaria surveillance and control. A nationwide school malaria survey was carried across the different malaria ecologies in Kenya. These data allowed analysis in different settings of risk factors for *Plasmodium* infection and anaemia and the evaluation of alternate malaria diagnostic methods. A cluster randomised trial was conducted in coastal Kenya to evaluate the effectiveness of school-based distribution of mosquito nets. Finally, the congruence between reports of net use from school and household surveys was evaluated.

Prevalence of *Plasmodium* infection was low overall, but varied markedly across the country. Risk factors for *Plasmodium* infection and anaemia varied by malaria transmission zone, with net use associated with reduced odds of infection in only coastal and western highland epidemic zones. The school-based distribution of mosquito nets was associated with an increase in reported net use but had no impact on *Plasmodium* infection or anaemia. In terms of identifying infection among individuals and populations, malaria rapid diagnostic tests represent a cheap diagnostic approach, especially in low and high prevalence settings. School surveys can also provide a reliable estimate of net use among both school children and households.

Collectively, these results highlight the burden of malaria among Kenyan school children but show how this burden varies by transmission setting, emphasizing the need for a geographically targeted approach to tackling malaria. The results also demonstrate the role that schools can play in the surveillance and control of malaria.

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ACT	Artemisinin Combination Therapy
ACT	artemisinin-based combination therapy
ANC	Antenatal clinic
AQ	Amodiaquine
AS	Artesunate
CDC	Centers for Disease Control and Prevention
CI	Confidence intervals
DDT	Dichlorodiphenyltrichloroethane
DfID	Department for International Developemnt
DHS	Demographic health surveys
DoMC	Division of Malaria Control
DVBND	Division of Vector Borne and Neglected diseases
EAs	Enumerations areas
EIR	Entomological inoculation rate
ELISA	Enzyme-linked immunoabsorbent assay
EPI	Expanded programme on immunization
ESACIPAC	Eastern and Southern Africa Centre of International Parasite Control
FEWS	Famine early warning systems
FPR	False positive rates
GLLAMM	Generalized linear and latent mixed models
GMEP	Global Malaria Eradication Programme
Hb	Haemoglobin
HRP-2	Histidine rich protein 2
IEC	Information, Education and Communication

IPT	Intermittent presumptive treatment
IRS	Indoor residual spraying
IST	Intermittent screening and treatment
ITNs	Insecticide treated nets
KEMRI	Kenya Medical Research Institute
LLIN	Long lasting insecticidal nets
LQAS	Lot quality assurance sampling
LSHTM	London School of Hygiene and Tropical Medicine
MERG	Monitoring and Evaluation Reference Group
MICS	Multiple indicator cluster surveys
MIS	Malaria indicator survey
MoE	Ministry of Education
MoPHS	Ministry of Public Health and Sanitation
NER	Net enrolment rate
NMS	National Malaria Strategy
NPV	Negative predictive values
PCR	Polymerase chain reaction
PDAs	Personal digital assistants
PfPR	*P. falciparum* parasite rate
pLDH	*Plasmodium* lactate dehydrogenase
PPV	Positive predictive values
PR	Parasite rate
PSI	Population Services International
R_0	Basic reproductive number
RBC	Red blood cell
RBM	Roll Back Malaria

RDTs	Rapid diagnostic tests
RUMA	Rapid Urban Malaria Appraisal
SCR	Sero-conversion rate
SD	Standard deviation
SMA	Severe malarial anaemia
SP	Sulphadoxine pyrimethamine
SSA	Sub-Saharan Africa
TNF-α	Tumour necrosis factor-α
UNICEF	United Nations Children's Fund
WHO	World Health Organisation
ZIP	Zero inflated Poisson

Chapter 1: Introduction

1.1. Background and context

The world malaria map has been shrinking[1]. During the first half of the 20th century, malaria endemic countries were involved in various malaria control efforts which peaked with the World Health Organisation's (WHO) launch of the Global Malaria Eradication Programme (GMEP) worldwide. Although almost all African states took up malaria control after the WHO's recommendation in the 1950 Kampala malaria conference, eradication was completely abandoned in Africa due to what the WHO described as 'high endemicity and weak infrastructure' to achieve eradication[1, 2]. Consequently, the funding for malaria control in Africa reduced and in the late 1980's to the 1990's malaria morbidity and mortality peaked again partly due to the failing antimalarials and abandoned control efforts[1]. Following recognition that malaria morbidity and mortality was rising in Africa, the Roll Back Malaria (RBM) initiative was launched in 1998 to coordinate malaria control efforts. Two years later in 2000, the African heads of state met in Abuja and resolved to half malaria mortality by 2010 by ensuring that 60% of at risk populations were protected with locally appropriate methods and treated for malaria[3].

Consequently, in the last decade, there has been significant progress in malaria control as a result of increased political commitment, funding and access to malaria control interventions[4, 5]. For example, funding for malaria control increased from an estimated US$ 35 million in 2000[6] to approximately US$ 2.5 billion in 2010[7, 8]. These funds have supported the expanded delivery of key malaria interventions including insecticide treated nets (ITNs), improved malaria diagnostics, artemesinin-based combined therapies (ACT), indoor residual spraying (IRS), and intermittent preventive therapy in pregnant women (IPTp).

The investments in malaria control are now beginning to be translated into improved coverage rates and health gains. For example, analysis of national sample survey data from 40 malaria endemic countries in Africa showed that ITN coverage among children aged under five years increased from 1.8% in 2000 to an estimated 18.5% in 2007[9]. By 2010, all of the 42 malaria endemic countries in Africa had switched to ACTs as first-line treatment[5]. Concomitantly, reductions in malaria morbidity and mortality have been documented in several countries including Kenya[10-13], Rwanda[14, 15], The Gambia[16], Eritrea[17], Zanzibar[18, 19] and in other countries in Africa[20-22].

Despite such progress, millions of people at risk of malaria remain unprotected and very few countries have achieved the 2010 targets of universal coverage with key interventions[9, 23]. Estimates from 2010 indicate that only 35% of African children aged under five years living in malaria endemic areas were sleeping under an ITN[23]. Even in countries that have undertaken recent ITN distribution campaigns aimed at universal coverage such as Tanzania[24], Senegal[25] and Sierra Leone[26], estimates indicate that only 56%, 46% and 72% of children under the age five years sleep under ITNs respectively. Such rates need to be increased to over 80% if there is to be an impact on malaria transmission, as suggested by mathematical modelling[27]. Moreover, until recently, malaria control interventions were justifiably targeted to only the most vulnerable groups (children under the age of five years and pregnant women), resulting in inequitable coverage of interventions, with school age children (5-14 years) being the least protected by control interventions[23, 28]. Yet, regardless of malaria transmission settings, school-age children have the highest levels of infection[29-32] and thus represent the largest reservoir of infections and are a significant contributor of human to mosquito infections[33]. To achieve tangible progress in malaria control in most countries, there is need therefore to scale up intervention coverage in all populations at risk including school-age children. It is estimated that over 80% of human to mosquito infections originates from children over the age of five years and adults who harbour the highest prevalence of infections which are likely to be untreated[34]. As well as contributing to overall transmission, *Plasmodium* infection among school-aged children may additionally cause anaemia[35, 36] and result in late school enrolment, absenteeism, poor cognitive performance and low educational achievement[37-44]. The precise burden of malaria among school-age children is poorly defined however.

To reliably estimate the burden of malaria among school-aged children there is a need for monitoring and surveillance tools which can guide decisions on appropriate intervention strategies. Currently, malaria surveillance, monitoring and evaluation, is mainly based on either periodic national level household surveys or health facility data, which typically collect data both on children under five years and pregnant women. The current malaria surveillance tools are not without their limitations. The household-based surveys are conducted only periodically (every 2-5 years), expensive, time consuming and require complex sampling procedures, while the health facility based data are mostly incomplete and unreliable[45]. School-based surveys of malaria can provide useful information on the burden of malaria among school children but may also provide a complementary, potentially cheaper, more rapid and regular malaria surveillance platform[46]. Although school surveys were a routine feature of historical, especially colonial, malaria surveillance, more recent experience in school malaria surveys is limited. The use of school surveys to describe the epidemiology, disease burden and control of malaria among school children and the wider community, as well as possible approaches to malaria control through schools, is the subject of this thesis.

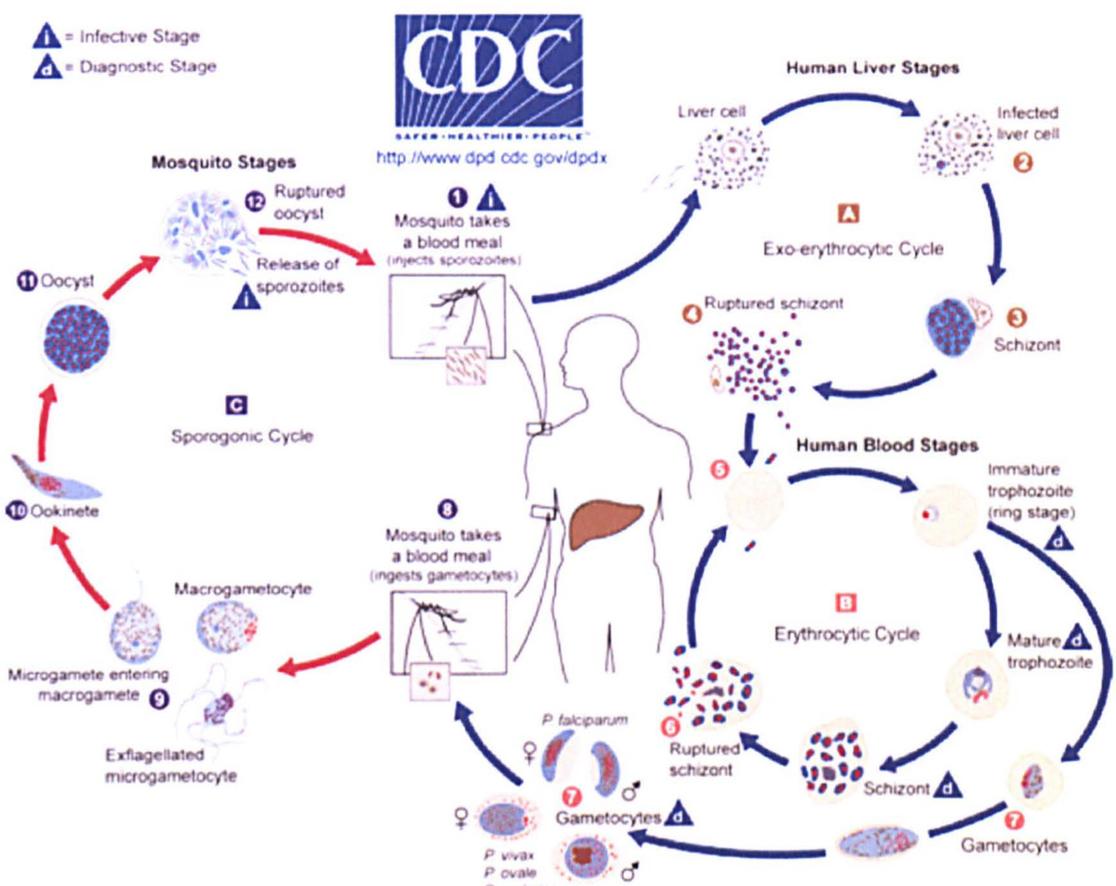
This chapter provides a brief introduction on specific topics that provide contextual information to this thesis including the biology of infection and pathological processes. Further information on the transmission and epidemiology of malaria, available control tools, diagnostic tools and the available surveillance tools is provided. The relevant aspects to malaria control in school-age children and malaria surveillance are also discussed.

1.2. Biology of infection

1.2.1. Parasite lifecycle

Malaria is a protozoan infection caused in humans by five *Plasmodium* species namely; *P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi.* Of these malaria species, *P. falciparum* is the most virulent, the most common species in Africa and is the main focus of this thesis. Malaria is predominantly transmitted through a bite from an infected female *Anopheles* mosquito but can also be transmitted through congenital transmission or through transfusion with infected blood. The development of the malaria parasite occurs in two stages: 1) the asexual stage in the human host; and 2) the sexual stage in the mosquito. Figure 1.1 presents the parasite's life cycle. The asexual stage begins with the inoculation of a sporozoite from the mosquito salivary glands to the human host. Once in blood, the sporozoites migrate to the liver after a period of thirty minutes to four hours and invade hepatocytes where they begin replicating. This replication stage is called the exoerythrocytic or pre-erythrocytic stage. Asexual multiplication takes place in the hepatocyte and the infected hepatocyte raptures releasing thousands of merozoites into the blood stream. In *P. ovale* and *P. vivax* infections a proportion of the parasites remain dormant in the liver and are therefore responsible for the relapsing form of malaria.

Figure 1.1: Malaria parasite life cycle, adopted from the Centre for Disease control's (CDC) website, accessed December 2012. (http://www.dpd.cdc.gov/dpdx/HTML/Malaria.htm).



The merozoites liberated into the blood stream rapidly invade erythrocytes and once inside the erythrocytes, they develop into young trophozoites which can be seen as ring forms under a microscope in Giemsa stained blood smears. The trophozoites mature and increase in size and the ring form morphology disappears. The mature trophozoites develop into schizonts in which merozoites develop. The infected erythrocyte then raptures releasing new merozoites into the blood which then re-infect other erythrocytes. In *P. falciparum* malaria the trophozoite and schizont-infected erythrocytes adhere to capillary endothelial cells and this sequestration is associated with cerebral malaria. After a series of asexual cycles, some of the merozoites develop into sexual forms (gametocytes), which then infect mosquitoes. The erythrocytic stage parasites are responsible for the pathology and clinical illness associated with malaria, as discussed in the following section.

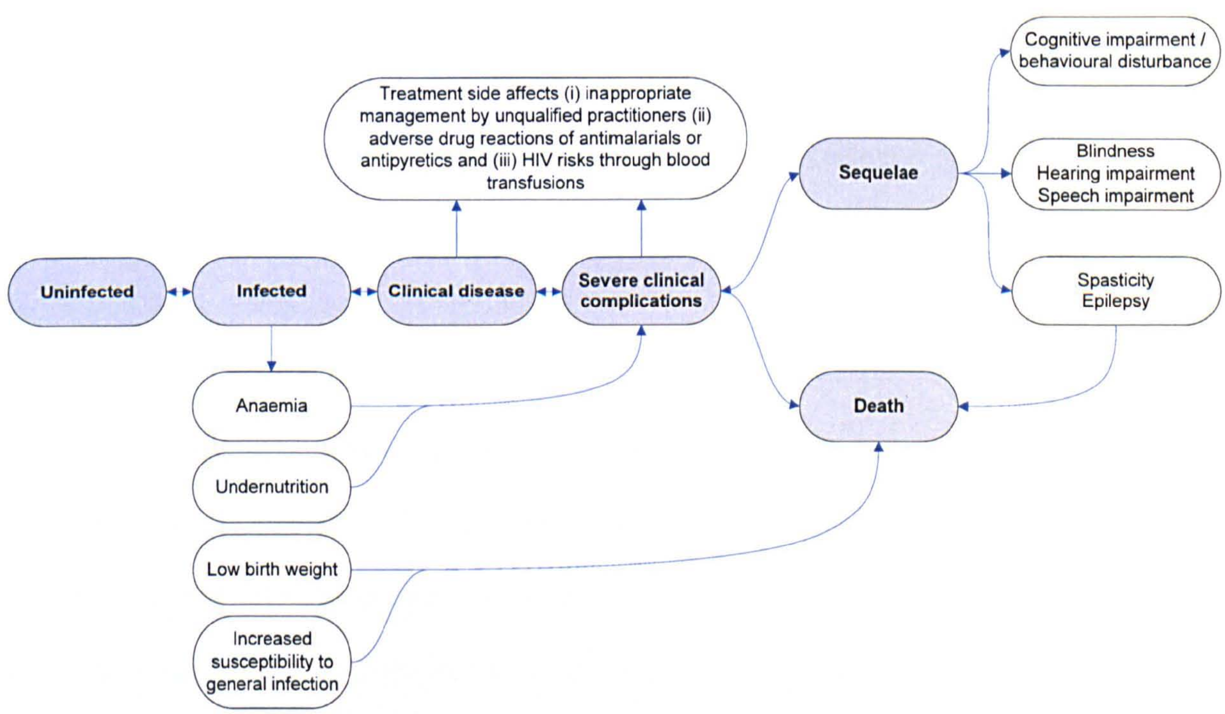
The sexual stage starts after the gametocytes are ingested by a mosquito. The male (microgamete) and the female (macrogamete) become activated in the mosquito's gut and the microgamete undergoes rapid nuclear division and each of the eight nuclei formed associates with a flagellum. The microgametes separate and seek the macrogametes after which fusion and meiosis takes place to a zygote. The zygote develops into a motile ookinete which penetrates the mosquito's mid gut and encysts becoming an oocyst. The oocysts then undergo asexual multiplication in a process called sporogony. The oocyst then bursts to release motile sporozoites into the ceolomic cavity of the mosquito which then migrate to the mosquito's salivary glands awaiting inoculation to next human host.

The success of the sporogony stage is critical in malaria transmission and is often used as the basis of entomological indices of malaria transmission intensity measurement as discussed in the subsequent sections.

1.2.2. Pathology of infection

Malaria pathological processes are related to the development of asexual parasites in blood and their interactions with host immunity and a variety of consequences can arise (Figure 1.2)[47]. After infection with malaria parasites some individuals may remain asymptomatic mainly due to acquired immunity[48], while others develop clinical illness that typically presents with fever. The clinical illness may resolve with or without medical interventions, and a small proportion of the clinical events develop into severe disease which may include severe anaemia, respiratory distress or altered consciousness (cerebral malaria). Some of the severe disease events may resolve, or may result in neuro-cognitive impairment or death[47].

Figure 1.2: Malaria pathology process. Adapted from ref[47]. The blue boxes represent the likely direct consequences of a malaria infection while the white boxes represent the likely indirect consequences of a malaria infection. The arrows represent the pathological processes and the relationship between the direct and indirect consequences of malaria.



1.2.2.1. Asymptomatic infections

A significant proportion of individuals infected with malaria remain asymptomatic due to exposure related acquired immunity. Several immunoepidemiological studies in areas of varying transmission intensities have demonstrated that the development of immunity against *P. falciparum* malaria infection and against symptomatic disease depend on malaria transmission intensity and on age[49, 50]. A recent review on the relationship between anti-merozoite antibodies and the incidence of symptomatic malaria, showed up to 54% reduction in the risk of symptomatic malaria in individuals with antibody responses compared to those without, with evidence of a dose response relationship[51]. In high transmission areas, a large proportion of infections are asymptomatic; for example in a study conducted in a high transmission area in The Gambia[52] reported up to 90% of infections being asymptomatic, with the highest prevalence (61%) in the school age population. High levels of asymptomatic infections have also been reported in moderate and low transmission areas[53, 54]. For example, a nationwide study in São Tomé and Príncipe where transmission is low, reported over 90% of infections being asymptomatic[54]. The true prevalence of asymptomatic infections remains unclear however, due to a limited number of studies and sub-microscopic infections that are undetected using microscopy (see section 1.6.1).

The occurrence of asymptomatic infection, although not causing severe morbidity or mortality, can have a number of consequences. The asymptomatic infections often go undetected and therefore untreated, and as a result are important contributors to anaemia, under-nutrition, low birth-weight and mosquito infectivity[55]. Anaemia is positively correlated with *P. falciparum* infection prevalence and parasite density[56]. Moreover, the presence of other concomitant anaemia aetiologies such as hookworm infection, schistosome infection (*Schistosoma haematobium and S. mansoni*) and malnutrition have been shown to synergistically increase the risk of anaemia[57, 58]. The mechanisms by which malaria causes anaemia are multiple and complex, but are principally due to increased erythrocyte destruction and decreased red blood cell (RBC) production[59, 60]. Increased erythrocyte destruction may be caused by: 1) phagocytosis of parasitized RBCs by macrophages in the reticulo-endothelial system; 2) rupture of the parasitized RBCs in the erythrocytic stage; and 3) destruction of non-parasitized RBCs. Suppression or infective erythropoesis have been suggested to cause decreased RBCs production[61]. In acute infections, children have been shown to have normal or fewer numbers of erythroid precursor cells suggesting transient suppression of the response to erythropoietin while in chronic or repeated infections there is erythroid hyperplasia leading to morphological changes in the precursor cells. In addition to increased RBC destruction and production suppression, it has been suggested that asymptomatic infections also inhibit iron absorption[62].

1.2.2.2. Clinical disease

Uncomplicated clinical disease due to *P. falciparum* infection is typically characterised by cyclic fevers and chills that are linked to the erythrocytic stage in the parasite life cycle. These symptoms are believed to be caused by malarial toxins released during the erythrocytic cycle that induce macrophages to secrete cytokines such as interleukin-1(IL-1) and tumour necrosis factor-α (TNF-α).

Plasmodium infections can progress to severe disease which is characterised by one or a combination of severe anaemia, metabolic acidosis, which is often associated with respiratory distress, or cerebral malaria, which in some cases can be fatal. An important consequence of malaria, especially in young children, is severe malarial anaemia (SMA), defined as haemoglobin (Hb) concentration of less than 5g/dL in the presence of malaria parasitemia. SMA is generally a disease of young children and has been shown to have a peak age of between 1 and 2 years[63, 64] with the highest burden in areas of high transmission intensity[11].

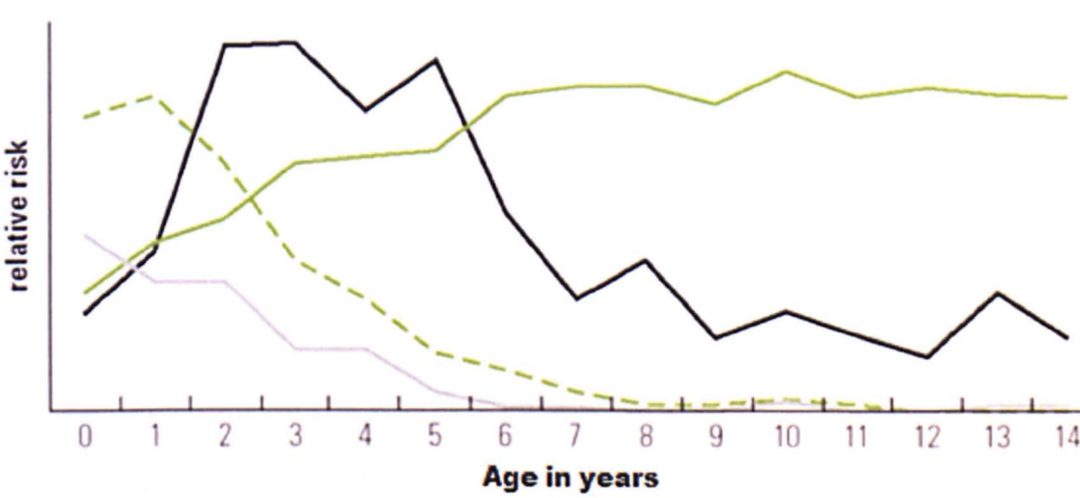
Cerebral malaria is the most life-threatening complication of *P. falciparum* malaria and is characterised by a coma. The altered consciousness in cerebral malaria has been attributed to the sequestration of parasitized erythrocytes in the cerebral micro-vasculature[65, 66], although some authors have attributed it to the release of inflammatory cytokines and metabolic factors[67]. Sequestration occurs through cytoadherence of parasitized erythrocytes to the endothelial lining and is further increased when the infected erythrocytes bind to other parasitized and non-parasitized erythrocytes or use platelets to bind other parasitized erythrocytes. Sequestration impairs brain perfusion and may cause hypoxia. About 20% of children admitted to hospital with cerebral malaria die, while the survivors may develop neuro-cognitive impairments which include quadriparesis, hemiparesis, speech/language difficulties, hearing and visual impairment, behavioural problems and epilepsy[68-70]. Unlike SMA, the highest burden of cerebral malaria is in areas of low to moderate malaria transmission and lowest in high transmission intensity[71].

1.3. Epidemiology and burden of disease

Across Africa, over 700 million people were estimated to be at any risk *P. falciparum* malaria in 2010[72]. However, the specific risks of infection, clinical disease, severe disease and mortality are age-specific and influenced by the underlying intensity of malaria transmission[63, 71, 73]. Specifically, the risk of infection increases with age while the risks of clinical disease, severe disease and mortality are subsequently reduced with increasing age as immunity to malaria is acquired (Figure 1.3).

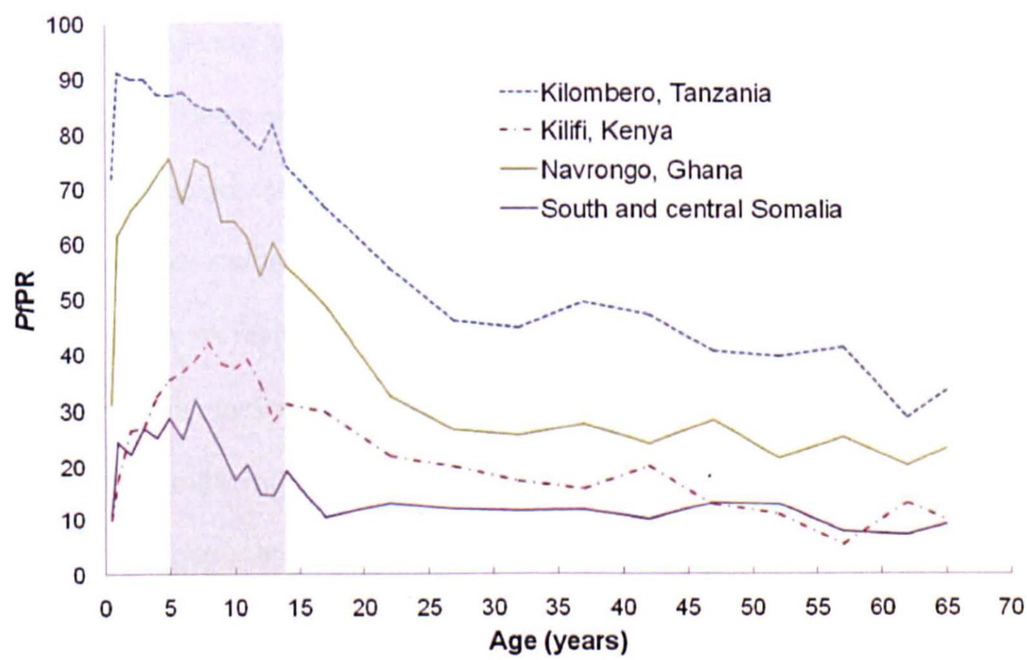
The rate at which exposure dependent immunity is acquired and therefore the burden of disease and the observed disease pathology in the population is critically dependent on the intensity of malaria transmission[73]. In high transmission settings, the risk of severe disease and mortality is highest in children under the age of five years due to the lack of functional immunity. Whereas in low transmission settings, where individuals have reduced exposure and have not developed adequate immunity, the risks of diseases are spread more evenly across age groups.

Figure 1.3: Age-structured risk of infection, clinical disease, morbidity and mortality due to *P. falciparum* for a population living at the Kenya Coast; adapted from ref[70]. The solid green line represents the relative risk of infection, the solid black line risk of morbidity, dashed green line risk of severe disease and the solid grey line risk of mortality.



In contrast to the age pattern of morbidity and mortality risks, the prevalence *P.falciparum* infection (*Pf*PR) exhibits a typical age-specificity across different transmission settings: *Pf*PR rises with age until the age of 2 years after which it plateaus up to the age of 10 years and then declines in adolescence through to adulthood[31] (Figure 1.4). Such age-specificity of infection is important in malaria surveillance (see section 1.5.1).

Figure 1.4: The relationship between *P. falciparum* parasite rate (PfPR) and age. The lines represent *Pf*PR by age in different populations with varying transmission intensity and the area shaded grey represents the typical age range for primary school children in Africa, adopted from ref[46].



1.3.1 Burden of disease in school age children

The burden of malaria in school age children is poorly defined. Recent estimates on the population at risk of *P. falciparum* malaria worldwide in 2010 based on geostatistical models, indicate that over 200 million children between the ages of 5 and 14 years in Africa are at any risk of *P. falciparum* malaria[72]. Although malaria morbidity and mortality among school age children is relatively low, the recent reductions in malaria transmission in some countries in Africa may result in later acquisition of exposure dependent immunity and therefore potentially increase the risk of disease in the school age population[71, 74, 75]. However, at country levels, there are few empirical data on the epidemiology of malaria in school age children to inform control and future surveillance.

The majority of malaria infections among school age children are asymptomatic, however such infections are important causes of anaemia in school age children[58]. In studies in school children in Zimbabwe and Kenya in areas of moderate to high malaria transmission intensity, *P. falciparum* infection was associated with 0.9g/dl and 0.16g/dl lower mean haemoglobin (hb) concentration in infected children compared to the uninfected respectively[57, 76]. Although these studies were cross-sectional and may not adequately capture the impact of malaria on anaemia, due to the transient nature of the infection, other studies have demonstrated that malaria control improves haemoglobin concentration. A review by Korenromp and colleagues on the impact of malaria control on anaemia, demonstrated that malaria control resulted in a mean increase in haemoglobin of 0.76g/dl across 28 studies in children under the age of five years in Africa[35]. Among school-aged children, a number of studies have demonstrated that treatment of asymptomatic infections significantly reduces the prevalence of anaemia[77-79]. For example, a study assessing the impact of IPT in school children in Kenya showed that treatment of asymptomatic infections once a term halved the prevalence of anaemia treatment group[77]. However, the impact of malaria control on anaemia is dependent on the malaria transmission intensity[35, 56] and the presence of other anaemia causative factors[58].

Clinical disease is most common in young children (Figure 1.3), however it is estimated that among African school-aged children living in areas of *P. falciparum* transmission the incidence of clinical malaria ranges from 20 to >50% per year in children[80]. Such clinical attacks are an important cause of absenteeism and therefore poor educational achievement in school children[81-83]. In Kenya, malaria was estimated to cause 4-10 million school days annually [81], while studies conducted in Sri Lanka have shown an association between clinical malaria attacks in school children, absenteeism and educational performance[40, 41, 84]. In the Sri Lankan studies, children who were diagnosed with clinical malaria had significantly lower academic scores and malaria control through weekly chemoprophylaxis using chloroquine reduced malaria-related absenteeism by 62%.

Although cerebral malaria mainly occurs in children under the age of five years, it has been shown to cause long-term neuro-cognitive impairments that consequently affect learning and educational achievement in older children[39, 42, 85]. Cerebral malaria is estimated to affect about 785,000 children under the age of nine years annually[86] and at least 1,300-7,800 of these children will have neurological sequelae following cerebral malaria annually in stable malaria endemic areas[87]. Although most the neurological complications resolve within six months of infection, some of them persist and result in long-term cognitive deficits[86, 88]. A retrospective study in Kenya compared children who had been admitted to hospital with cerebral malaria or malaria with complicated seizures nine years earlier with children unexposed to either condition[88]. Each child underwent a battery of tests on cognition, hearing, vision, speech and language. Children who had suffered cerebral malaria and malaria seizures were twice as likely to have at least one of the neuro-cognitive impairments assessed compared to the unexposed children. In addition, children with cerebral malaria were more likely to have multiple impairments and children who had low cognitive functioning were not enrolled in school. Moreover, children who suffer from cerebral malaria in the school age years are also likely to have cognitive deficits. For example, in a case-control study in Uganda compared children aged between 5-12 years presenting at a tertiary level hospital with cerebral malaria, with children with uncomplicated malaria and healthy community controls, and reported that children who had suffered cerebral malaria were 3.67 times more likely to have cognitive deficits after two years of follow-up compared to the healthy children in the community[42].

Despite the lower rates of clinical malaria in adolescence (Figure 1.3), it is estimated that 50% of first pregnancies in many malaria endemic countries in Africa occur in teenagers[89]. For example, in a recent study in rural Burkina Faso 76% of primigravidae women attending antenatal clinics were below the age of 19 years[90]. While all pregnant women are at an increased susceptibility for malaria, several studies have shown that adolescent primigravidae women are at a higher risk of malaria which has both maternal and fetal consequences[91]. Factors such as low immunity, late presentation to ANC clinics and lack of adherence ANC visits significantly increase the risk of malaria and adverse maternal and fetal outcomes in teenage pregnant women[90, 91]. A review by Guyatt and Snow in 2001[92], revealed a child was twice as likely to born with low birth weight if the mother had an infected placenta at the time of delivery and that the probability of death in the first year of life was three times higher in low birth weight babies compared to normal birth weight babies in Africa. In addition children born of low birth weight have been shown to be at higher risk of developmental and cognitive deficits later in life[91].

Encouragingly several effective malaria control tools are available for malaria control in school children[93] but effective implementation of malaria intervention requires a rigorous understanding of the efficacy of the available malaria control tools in different transmission settings. The next section describes the available malaria control tools and evaluates the impact of these tools among school age children, either implemented in schools or through the wider community.

1.4. Available malaria control tools

Several effective interventions are available to control malaria, including ITNs, IRS, IPT and prompt treatment with ACTs.

1.4.1. Insecticide treated nets

ITNs have been proven to protect against malaria morbidity and mortality in children under the age of five years and pregnant women: pooled results from efficacy trials conducted in the late 1980's and 1990's, indicated a protective efficacy of 18% from all cause child mortality and a 50% reduction in clinical malaria cases in children under the age of five years[94]. Under operational conditions, ITNs have also been shown to effectively reduce mortality and morbidity[95]. In Kenya, for example, a study evaluating the effectiveness of bed nets on malaria mortality in four districts with different malaria transmission patterns, showed a 44% reduction in mortality in children under the age of five years[96]. A pooled analysis of seven national household based surveys in seven sub-Saharan Africa (SSA) countries showed a 24% reduction in the risk of parasitaemia in children under the age of 5 years who were reported to use an ITN the night before the survey[95]. In recent years, a reduction in malaria transmission in several African countries has partly been attributed to the increase in malaria control interventions such as ITNs, with studies in Kenya, The Gambia, Rwanda, Eritrea and Zanzibar reporting reductions in malaria transmission with increasing ITN coverage [13, 14, 17, 18].

1.4.2. Indoor residual spraying

The use of IRS for malaria control has a long history that dates back from the pre-eradication era[1, 97]. During the WHO global malaria eradication programme, spraying with dichlorodiphenyltrichloroethane (DDT) was instrumental in the eradication of malaria in many non-African countries[1]. IRS works by both repelling mosquitoes from entering houses and by killing mosquitoes that rest on the walls after a blood meal therefore reducing transmission. In 2009, 27 countries in Africa were implementing IRS as part of their malaria control activities[23], resulting in demonstrable reductions in malaria transmission[98-103]. In a recent review, IRS was shown to reduce incidence and prevalence of infections[102], while a study in Kenya evaluating the impact of targeted IRS in highland epidemic transmission regions demonstrated that IRS reduced the monthly malaria prevalence in school children by half over a 12 month period and at the same time reduced the incidence of clinical disease and vector densities[99]. IRS and ITNs have been recommended as complementary tools for malaria control in high transmission settings[104], and a recent study in a high transmission area in western Kenya demonstrated a 61% reduction in *P. falciparum* parasitemia in individuals who used a combination of ITN and IRS compared to those who used ITNs only[101].

1.4.3. Intermittent Presumptive Therapy (IPT)

IPT involves periodic mass administration of a full therapeutic dose of antimalarials to certain high risk groups in high transmission areas. Several strategies of IPT are available including IPT for pregnant women (IPTp), IPT for infants (IPTi), IPT for children (IPTc) and IPT for school children (IPTsc)[105]. IPTp involves sulphadoxine pyrimethamine (SP) administered during antenatal visits and is aimed reducing peripheral parasitemia, placental malaria, anaemia and therefore the risk of low birth weight. Several studies have demonstrated that IPTp using SP reduces the risk of low birth weight, placental malaria, anaemia and peripheral parasitemia[106-109]. Although some studies have shown that IPT-SP continues to be beneficial even in areas with reported SP resistance[110], other studies have reported reduced IPT-SP efficacy in areas with SP resistance necessitating trials on efficacy of alternative drugs[111]. Alternative drugs such as mefloquine have been shown to more efficacious than SP however they are less tolerated in pregnancy[109]. The majority of countries in Africa currently have policies on IPTp, but effective coverage remains low[112].

IPTi is usually given at routine contact times with the health system such during infant vaccinations and is aimed at reducing prevalence of infection and anaemia[105, 113]. A pooled analysis of 6 randomised control trials assessing the impact of IPTi delivered during immunization indicated that IPTi had a protective efficacy of 30.3% against clinical infection, 21.3% against anaemia and also reduced hospital admissions[114]. IPTc is aimed at older children with the purpose of reducing clinical disease and malarial anaemia; however the main challenge of IPTc is implementation since it happens outside the expanded programme on immunization (EPI)[105]. IPTc has been shown to be efficacious against parasitemia, anaemia and clinical disease[115]. A recent review on the effect of IPTc on malaria in children under the age of five years living in endemic areas with seasonal transmission showed that IPTc prevented by over 70% of clinical malaria episodes and severe malaria cases in West Africa[115]. IPT has also been provided to school children – see section 1.4.5.

1.4.4. Prompt treatment of cases using artemesinin combination therapies (ACTs)

Prompt access to malaria treatment with effective antimalarials is one of the principal malaria control strategies recommended by the WHO global malaria programme. Currently, ACTs are recommended by the WHO for the treatment of uncomplicated *P. falciparum* malaria, replacing failing antimalarials drugs used previously[116]. Presently, all malaria endemic countries in Africa recommend ACTs for the treatment of malaria, however prompt access to ACTs for the treatment of malaria remains low[117]. Several measures aimed at improving prompt treatment using ACTs have been employed including the use of community health workers to treat malaria[118, 119], deployment of highly subsidised ACTs in the private health sector[120], health education campaigns[121] and treatment by school teachers[122, 123] have been shown to be useful.

1.4.5. Impact of malaria control interventions on school age children

Whilst, there is a wealth of evidence on the efficacy and effectiveness of the above malaria interventions on young children and pregnant women, there are fewer data on the efficacy of malaria control interventions among school age children.

In the case of ITNs, a 1988 randomised trial in Kenyan school children between the ages of 6 and 18 years showed that the use of untreated mosquito nets following anti-malarial treatment reduced the risk of new infections by 97.3%, but did not reduce anaemia[124]. Another community based randomised control trial in Western Kenya assessed the impact of ITNs on malaria and anaemia on adolescent girls aged 12 to 18 years. In this trial ITNs halved the prevalence of mild all-cause anaemia in 12 and 13 year olds but there was no impact on malaria parasitemia or on anaemia in older girls[125]. Possible

explanations are that older children may have already developed immunity to malaria infections and unlike in the earlier study where net use was directly observed, reported use of nets may have introduced bias. More recent analysis of cross-sectional survey data suggest that net use among school-aged children is associated with 71% and 43% lower risk of *Plasmodium* infection in Somali[126] and Ugandan[127] children, respectively.
The scaling up of ITN coverage in moderate to high transmission settings and encouraging use is likely to impact on malaria control in school age children. In the 2007 WHO position statement on ITNs[128], the WHO recommended universal ITN coverage of all age groups, including school-aged children. ITN programmes in Africa had previously been focused on children under the age of five years and pregnant women, which led to inequitable ITN coverage with children between the ages of 5 and 19 years being least covered[28]. In addition, factors such as sleeping arrangements, where school age children are less likely to sleep on a bed or in a sleeping area, have been documented as possible reasons for the low ITN use among children in the school age group[129, 130]. Moreover, the few school-age children who sleep under ITNs are likely to sleep under torn nets, as has been observed in studies in Kenya[131, 132]. To increase coverage and equity in ITN ownership and use, complementary ITN delivery strategies such as ITN distribution through schools using the existing school infrastructure are likely to improve coverage in the school age group[28]. However, the potential effectiveness of ITNs under operational conditions is likely is to vary according to malaria transmission intensity. The potential efficacy of ITNs in areas of varying transmission intensities will be explored further in this thesis.

The impact of chemoprophylaxis on malaria in school-age children has been assessed in a number of studies. Community-based chemoprophylaxis has been shown to have long term educational benefits for children who were protected early in life. A study in The

Gambia that followed up children who had participated in a chemoprophylaxis trial 14-16 years previously showed that educational attainment was better in the group that received chemoprophylaxis compared to the placebo group[43]. There were however no differences in cognitive abilities between the groups. A trial in Sri Lanka assessed the impact of chloroquine prophylaxis on malaria and educational attainment of school children. Weekly chemoprophylaxis with chloroquine was associated with a 50 percent reduction in the incidence of clinical malaria, decreased absenteeism and improved educational attainment[84]. At present, chemoprophylaxis is not recommended for local populations in malaria endemic areas.

An alternative to chemoprophylaxis given on a regular basis is IPT. A trial in western Kenya assessed the effect of school-based IPT on anaemia, malaria and education[77]. IPT using SP and amodiaquine (AQ) was provided once a term for three terms and was showed to dramatically reduce malaria parasitemia and anaemia (protective efficacy of 89% and 48% respectively) and significantly improved cognitive ability. IPTsc using SP-artesunate (AS) or AQ-AS has been shown to decrease the prevalence of asymptomatic parasitemia and anaemia in school children[77, 79, 124]. However, with the increasing SP resistance the utility of SP in IPTsc may be decreased especially in high transmission areas where the aim of IPTsc may be more of clearing asymptomatic infections rather than preventing new infections[105]. To address the issue of SP resistance some authors have proposed the screening and treatment of asymptomatic infections using ACTs and an ongoing study in Kenya is evaluating the health and educational benefits of intermittent screening and treatment (IST) using ACTs[133]. IPT and IST using ACTs are likely to be most applicable in high and moderate transmission settings where children harbour asymptomatic infections. At present, the optimal approach to drug-based interventions delivered through schools remains unclear.

School-based health education and the use of school teachers as service providers have been shown to improve access to prompt treatment of malaria. A study in Ghana in which teachers were trained on clinical malaria diagnosis and treatment of cases showed that teachers were able to correctly diagnose clinical malaria and promptly administer treatment[122]. Another study in Thailand showed that school-based health education on malaria increased the proportion of children who promptly reported having fever to their parents and teachers[121]. In Malawi, a school health and nutrition programme evaluated the programmatic use of presumptive treatment in 101 schools[123]. Started in 2000, the project trained teachers to treat malaria in schools using a Pupil Treatment Kit including SP. In each school, three teachers received training, including recognition of the signs and symptoms used to diagnose malaria and safe administration of antimalarial treatment. Sick children were reported to teachers and suspected malaria cases were treated with SP according to the national guidelines where antipyretics were provided to the sick children to take home. The overall and malaria-specific mortality rates for the 3 years before and 2 years after the intervention dropped from 2.2 to 1.44 deaths/1000 student-years and from 1.28 to 0.44 deaths/1000 student-years, respectively. Although successful, such school-based treatment programmes may have several limitations today. Teacher-based diagnosis of malaria may result in over diagnosis and therefore unnecessary treatment with the more expensive ACTs.

The optimal choice of the above interventions as well as their efficacy will crucially depend on the underlying malaria transmission intensity[104]. The next section discusses the different measures of malaria transmission.

1.5. Malaria transmission intensity

Malaria transmission intensity is measured using several malariometric indices including the parasite rate (PR), entomological inoculation rate (EIR), the basic reproductive number (R_0) and the malaria antibody sero-conversion rate (SCR). Such indices are used to classify endemicity to estimate level of malaria risk and to inform the planning of control.

1.5.1. Parasite rate (PR)

PR is a measure of the proportion of the surveyed population harbouring *Plasmodium* parasites in peripheral blood. In *P. falciparum* malaria, *P. falciparum* parasite rate (*Pf*PR) is the most commonly measured malaria transmission index, typically assessed using microscopy but increasingly with rapid diagnostic tests (RDTs) and polymerase chain reaction (PCR). The relationship between *Pf*PR and age makes it difficult to compare *Pf*PR measured in different age groups. Fortunately, mathematical models have shown that *Pf*PR in children between the ages of 2 and 10 years ($PfPR_{2\text{-}10}$) is optimal in measuring *P. falciparum* malaria endemicity and is related to other measures of malaria endemicity, including EIR and R_0[31]. In the global eradication programme the following classes were used to classify malaria risk: hypoendemic if $PfPR_{2\text{-}10}$ is less than 10%, mesoendemic if $PfPR_{2\text{-}10}$ is 11-50%, hyperendemic if $PfPR_{2\text{-}10}$ is 51 - 75%; and holoendemic if PR in the 1 year age group is constantly over 75%. Recently, $PfPR_{2\text{-}10}$ has been used both in the development of *P. falciparum* risk maps[72, 134] and re-defining transmission for malaria control and eventual elimination[104]. Hay and colleagues have suggested different classes of malaria endemicity classification based on prevalence of *Plasmodium* infection: < 1%, 1-4.9%, 5-39% and ≥ 40%, which reflect the underlying population dynamics, and potential efficacy of interventions and determine the appropriate suite of interventions for control[104].

*Pf*PR$_{2\text{-}10}$ has several advantages: first it is relatively constant between the ages of 2-10 years (Figure 1.4); second, it is relatively easy to measure in the field; third, older children suffer less from clinical malaria hence it is less likely to be affected by antimalarial drug treatment; and lastly, anti-parasitic immunity to malaria is less developed in this age group[31]. Consequently, malaria surveys in children between the ages of 2 and 10 years would be ideal for measuring malaria transmission intensity and the highest proportion of those children are in the school-age population as shown in Figure 1.4.

Although *Pf*PR is relatively easy and quick to measure and it defines infection status at the individual level, it crucially depends on the accuracy of tools used for diagnosing infection[31], (see section 1.6 for further discussion on the accuracy of the various diagnostic tools and its implications on malaria transmission intensity measurement). In addition, in low transmission settings, large samples are required for reliable measurement of PR due to scarcity of parasite positive individuals.

1.5.2. Entomological inoculation rate (EIR)

The EIR is the most direct measure of malaria transmission and is considered the 'gold standard' measure of malaria transmission. It is defined as the average number of infective mosquito bites received per person per year. The calculation of EIR is based on various measures: the biting rate which is the number of bites per person by 1 mosquito per day and the sporozoite rate which is the proportion of mosquitoes carrying sporozoites[135]. Although EIR is the most direct measure of transmission intensity, it is labour intensive and lacks standardized methods of measurement making it difficult to compare estimates over space and time[135, 136].

1.5.3. Basic reproduction number (R_0)

R_0 is defined as the number of infections arising from a single infected person in the absence of immunity and malaria control. The magnitude of R_0 determines if elimination is possible and the potential efficacy of malaria control interventions[137]. If R_0 is less than 1 the number of new infections decreases and therefore elimination would be possible, and if R_0 is greater than 1 the number of infections increases. The calculation of R_0 is based on the vectorial capacity (the number of secondary inoculations that arise from one infectious person per day) and the daily loss of infectivity. R_0 can also be calculated indirectly using the PR and EIR estimates; however the reliability of such calculation is dependent on the accuracy of the PR and EIR estimates. Estimation of R_0 and the vectorial capacity allows for the strategic planning of malaria control through interventions such as ITNs and IRS that increase vector mortality thus reducing transmission. However, R_0 is rarely calculated and those estimates that do exist do not normally take into account variations in vector behaviour, re-infection patterns and host susceptibility[137].

1.5.4. Sero-conversion rate (SCR)

SCR refers to the rate at which humans develop antibodies to the products of malaria infection and is a measure of malaria exposure over time, which has been shown to be related to the EIR[138, 139]. Its estimation involves the determination of antibody prevalence by age using enzyme-linked immunoabsorbent assay (ELISA) and the observed antibody prevalence is used to calculate the SCR. SCR has been shown to be a reliable tool in the estimation of transmission intensity and temporal changes in transmission in low transmission settings[138, 140, 141]. Unlike PR and EIR measures, which are affected by seasonality and availability of positive samples, SCR measures exposure to infection overtime and is therefore a relatively stable measure of transmission in low and unstable malaria transmission settings[139].

1.6. Parasite detection

The central role of parasite rate in the epidemiology of malaria makes it important to reliably estimate the prevalence and distribution of *Plasmodium* infection so that interventions are targeted to priority areas[104]. Estimation of prevalence relies on two key factors: (i) accurate methods of parasite detection; and (ii) optimal strategies to sample the population. For the diagnosis of malaria, a number of different techniques are available, including microscopy, rapid diagnostic tests (RDTs) and polymerase chain reaction (PCR). Each approach, however, has its own advantages and disadvantages.

1.6.1. Microscopy

The microscopic examination of Giemsa stained thick and thin blood smears for the detection of asexual blood stage parasites in the peripheral blood has long been considered the 'gold standard' to malaria diagnosis. The main advantage of microscopy is that it is able to detect parasite species and quantify the density of infection. Microscopy has a detection limit of 50-100 parasites per microlitre (μL) of blood[142], but this threshold has been shown to vary significantly depending on experience and training of the microscopist and the quality of reagents and equipment[142-147]. The main limitation of microscopy in epidemiological studies is the inability to detect sub-microscopic infections. A recent review compared the performance of microscopy to PCR and indicated that microscopy misses almost half of infections in field studies[146], reducing the ability of microscopy to reliably estimate infection status and consequently underestimates malaria transmission intensity. The use of microscopy in school malaria surveys may underestimate infection status due to the low density infections which are commonly harboured by school-aged children[53, 148].

1.6.2. Rapid diagnostic tests (RDTs)

In the last 15 years, a variety of rapid diagnostic tests, based on antigen detection through immunochromatography, have been developed and are now widely being used for malaria diagnosis. RDTs detect either histidine rich protein 2 (HRP2) specific to *P. falciparum* or *Plasmodium* lactate dehydrogenase (pLDH) or aldolase, enzymes which are common to all *Plasmodium* species. RDTs provide a simple, quick and cheap method for malaria diagnosis and can be used by individuals without formal laboratory training[149] and importantly, provide diagnosis quickly at the point of testing[142]. However, RDTs are not without their limitations, as they can miss infections especially in the detection of low parasite densities[150], especially in school-aged children[53, 148], and result in false positives. The occurrence of false positives is a particular issue for those RDTs that detect the histidine-rich protein-2 (HRP-2)[150-153]. Whilst such false positives of RDTs may have less importance for clinical case management, they will overestimate the true parasite prevalence compared to expert microscopy or molecular parasite detection techniques [142].

1.6.3. Molecular tests

Other test such as PCR, are also available. PCR tests are based on detection of parasite DNA and can be used for parasite detection and quantification. Real time PCR is commonly used because of its quick turnaround time. Real time PCR has a parasite detection threshold of up to 20 parasites/μL of blood[154] therefore making it more sensitive than microscopy and RDTs, and has been used widely for confirmation of infection in clinical and field studies. However, it requires expensive equipment, reagents and specialised training of laboratory staff compared to the use of microscopy or RDTs[155]. In low transmission settings and in individuals with low parasite densities, such as school-aged children, PCR may be a useful tool for reliable estimation of infection status. Recent studies have shown that pooling of samples for PCR in low transmission settings reduces the associated with costs of PCR while at the same time providing reliable prevalence estimates in epidemiological studies[156-158]. In the 2010 malaria indicator survey in Swaziland, employing a pooled PCR method reduced labour and consumable costs by over 95%[158].

1.7. Malaria surveillance approaches

In addition to accurate diagnostic strategies there is need for representative malaria surveillance platforms that can provide statistically reliable information on malaria burden and intervention coverage.

1.7.1. Household-based cluster surveys

One of the mainstay of malaria surveillance is household-based cluster surveys, including the malaria indicator survey (MIS)[159] as well as specific malaria modules in demographic health surveys (DHS)[160], and UNICEF's multiple indicator cluster surveys (MICS)[161]. The MIS was designed by Roll Back Malaria (RBM) Monitoring and Evaluation Reference Group (MERG) as a stand-alone survey to measure core RBM intervention coverage and morbidity indicators. The DHS was designed to collect data on wide range of health and demographic indicators and the MICS was designed by the United Nations Children's Fund (UNICEF) to help countries fill data gaps for monitoring the state of children and women in the areas of health, education, gender equality and rights. Although the DHS and MICS are not malaria specific surveys, they include optional malaria indicator modules for inclusion in malaria endemic countries. These household-based surveys involve a two stage sampling method. In the first stage, enumerations areas (EAs) from the national population census are used as the sampling frame. The EAs are then sampled with probabilities proportional to size. In each selected EA, a household listing is done and a fixed number of households are randomly selected according to the desired sample size. These surveys are done every 3-5 years using standard questionnaires allowing comparisons over time.

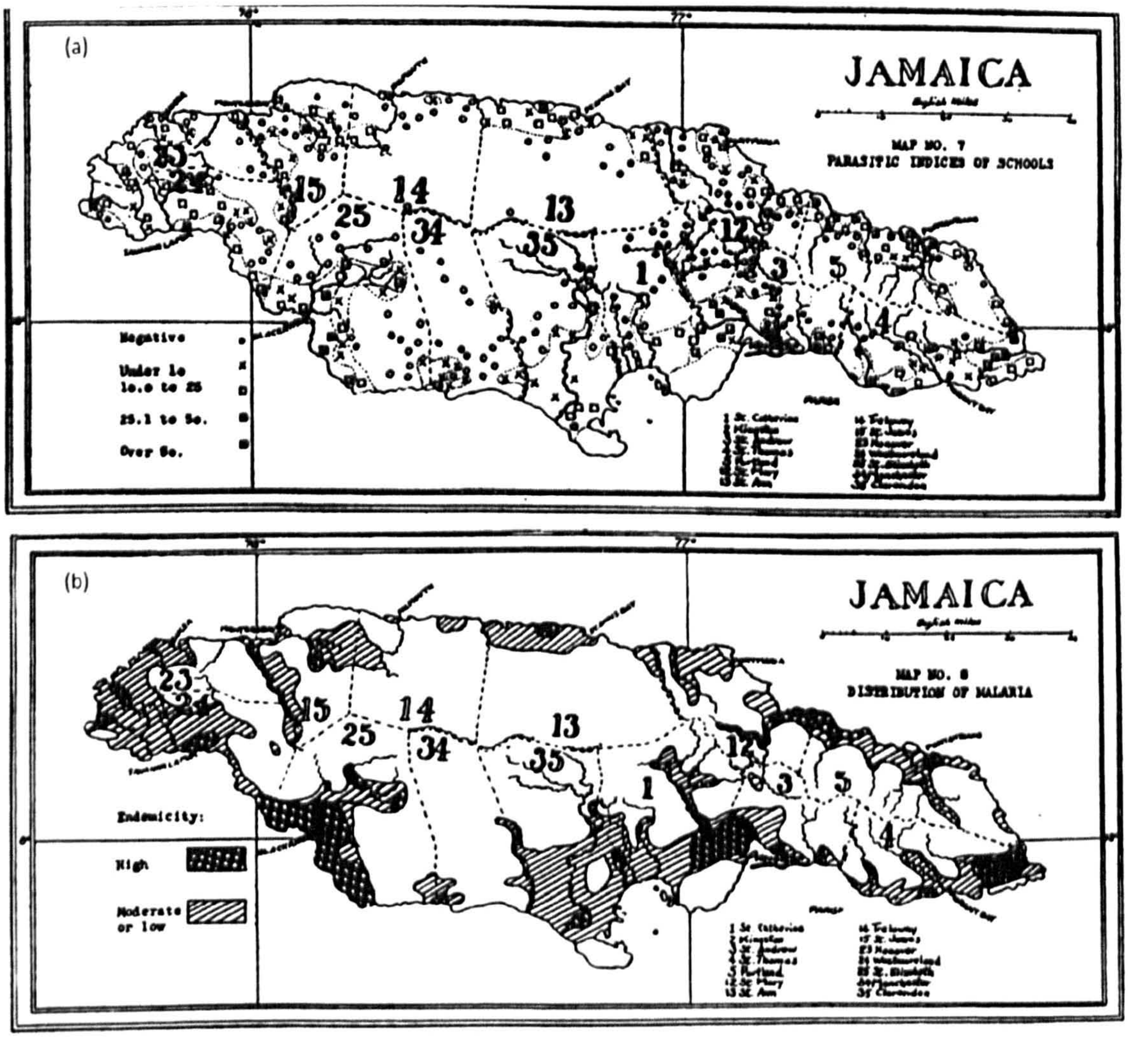
The MIS and the malaria modules in the DHS and MICS collect data on household ITN coverage, ITN use in children under the age of five years and pregnant women, IPTp use and prompt and effective treatment of malaria in children under the age of five years. Additionally, the MIS and some DHS include malaria parasitemia and anaemia testing in children under the age of five years. However, recent MIS, such as the Kenya 2010 and Swaziland 2010, have included malaria parasitemia and anaemia testing in older children. The main advantages of the household-based cluster surveys are that they provide reliable estimates of ITN, antimalarial and IPTp coverage because they allow for the direct observation of intervention uptake. Disadvantages of household surveys are that they are expensive, time consuming and, in many cases, are not statistically powered to provide sub-national estimates of infection prevalence and intervention coverage. In addition, these surveys are undertaken every 3-5 years and may not provide information on the real time changes in transmission and malaria intervention coverage. Some of these limitations can potentially be addressed by school-based malaria surveys, which can provide a complementary surveillance platform to household surveys.

1.7.2. School-based surveys

School malaria surveys can be used to define the burden of malaria in school-age children, but can also provide a complementary approach to household and health facility surveys [46]. School-based malaria surveillance is not a new approach, however. School-based malaria surveys formed an important part of malaria reconnaissance during the malaria pre-eradication period (Table 1). In Cuba, for example, nationwide school malaria surveys were undertaken between 1935 and 1942, sampling some 90,767 children nationally[162]. Similar surveys were done in El Salvador[163], the State of Veracruz in Mexico[164] and in Florida, United States[165]. In these surveys, investigations often involved a two-stage process in which all or a sample of children in a school would be examined for splenomegaly and then a subset of children, usually those with enlarged spleens and a random sample of those without palpable spleens would have blood smears collected for microscopy. These large-scale surveys were useful in describing the spatial distribution of malaria for control planning and tracking the impact of the malaria control activities. In Jamaica, school surveys were conducted in all government schools across the island in 1929 and were useful in describing the spatial risk of malaria in the island (Figure 1.5)[166] which later informed control planning. Schools were also used as sentinel sites for monitoring the impact of malaria control activities. In Punjab State in India, for example, a selection of 490 schools were used as sentinel sites to measure changes in malaria exposure over a 30 year period[167].

In Africa, large school malaria surveys were not routinely done mainly due to the under-developed road infrastructure and low school enrolment levels. However, small-scale school surveys were done as part of surveillance in Southern Rhodesia (now Zimbabwe) between 1937 and 1948 before they began insecticide spraying in 1949[168]. In the Bechuanaland Protectorate (now Republic of Botswana) school malaria surveys in the 1960's allowed for the spatial description of malaria endemicity in the country for malaria control[169]. Similarly, in Uganda school malaria surveys formed an important part of the malaria reconnaissance and programme evaluation in the late 1950s to the mid 1960s[170, 171]. In Kenya, school malaria surveys were routinely done for malaria surveillance by the Division of Vector Borne diseases (DVBD) since its establishment in the 1970s until the late 1990s when they were abandoned due to lack of funds[46, 172].

Figure 1.5: (a) The geographical distribution of *Plasmodium* infection in 422 schools, and (b) the geographical distribution of malaria endemicity in Jamaica in 1929, based on school survey results. (Taken from ref.[166])



Today, school malaria surveys are not done routinely and are not part of the core malaria surveillance and evaluation tools, but there are a few examples of school-based surveys conducted to answer specific research questions. In Madagascar, for example, school malaria surveys have been done to provide data for monitoring and evaluation of malaria control programmes[173-175]. In 1998, 13,462 school children from 170 schools were examined using both microscopy and serology in the highlands of Madagascar to evaluate an indoor residual spraying programme in the region[175]. School surveys have also been conducted as part of the Rapid Urban Malaria Appraisal (RUMA) methodology[176]. In 2003, the RUMA surveys were done in cities in Tanzania[177], Côte d'Ivoire[178], Burkina Faso[179] and Benin[180], and in each city 3 or 4 schools with different malaria endemicity were sampled and *Plasmodium* infection determined using microscopy. In addition to these malaria school surveys, lessons can be learnt from helminth epidemiology, where school surveys are regularly used to describe the epidemiology of infection and disease and for evaluating the impact of deworming programmes[181, 182].

Table 1.1: Tabulated summary of some of the historical school malaria surveys

Authors	Country and year of study	Sampling and diagnosis	No. examined
Boyd & Aris (1929)[166]	Jamaica (1928 - 1929)	• Surveyed all government schools in Jamaica. • 20-40 children per school, 5-14 years • Spleen examinations and microscopy • Microscopy on all children with splenomegaly and half of the children without splenomegaly	11,998 spleen examinations 6,445 microscopy examinations
Schwetz & Baumann (1929)[183]	Congo (May 1928 – February 1929)	• Malaria surveys in 10 schools • Spleen exams and microscopy for all children, aged 5-20 years	952 children had both spleen and microscopy examinations
Griffitts (1934)[165]	Florida, USA (1932 – 1933)	• School children in 136 schools in 8 counties in Florida • Sample included approximately 90% of rural school children • Microscopy only	9,275 children microscopy examination
Balfour (1935)[184]	Greece (1930-1933)	• Review of medical records (1921-1932)- reliability of records and diagnosis • Country-wide school malaria survey in 1933 • Spleen examination and microscopy for all children sampled, aged 5-14 years	8,184 spleen examinations 7,662 microscopy examinations
Uttley (1935)[185]	Hongkong (1933 - 1934)	• A school per village was sampled • Children were examined for enlarged spleens, aged 5-14 years	4,659 spleen examinations
Kumm & Ruiz (1939)[186]	Costa Rica (1939)	• All schools in the country but only 709/760 schools were located. • In villages where the schools were not large, children <12 years were rounded-up and examined • Enrolled and non-enrolled children in 168 localities nationwide were sampled and had spleen exams. Blood smears were collected for all children who had enlarged spleens and every third child with a non-enlarged spleen	9,126 spleen examinations 3,981 microscopy examinations

Table 1.1 continued

Authors	Country and year of study	Methods	No. examined
Carr &Hill (1942)[162]	Cuba (1935-1942)	• All public schools in the municipalities • 30 children per school • Age 5 - 14 years • Microscopy on all children with splenomegaly and every 2nd or 3rd child negative for splenomegaly	90,767 spleen examinations 42,320 microscopy examinations
Beet (1949)[187]	Central Province, Northern Rhodesia (now Zimbabwe) 1947-1948	• School surveys in 16 schools in two districts. • Children were conveniently sampled. • Examined haemoglobin concentration, malaria by microscopy, spleen examinations, stool examination and urine filtration for schistosomiasis	630 spleen examinations and microscopy
Castellanos et al. (1949)[164]	State of Veracruz, Mexico (1944-1946)	• All schools in the state with a minimum sample of 50 children per school • Age: 5 - 14 years • Spleen examinations on all children and microscopy on all children with enlarged spleens and 20% of those without palpable spleens	22,423 spleen examinations 7,019 microscopy examinations
Swaroop (1949)[167]	Punjab, India (1913-1943)	• All male children under the age of 10 years attending a sample of primary and secondary schools in Punjab • Spleen examination twice a year in June before the rains and in November after the rains for 30 years	An average of 68,000 children attending 490 schools were examined yearly
Che'n & Liang (1956)[188] TAMRI (1958)	Taiwan (1953 and 1955)	• 1st survey in 1953: Island wide survey of all 847 schools, 200 children per school • Follow-up surveys in 1955: Island wide surveys in schools that had shown the highest spleen rate in each township in the 1953 survey. • Age: 6-9 years	1953: 169,400 spleen examinations 1955: 66,444 spleen examinations
Davies & Vardy-Cohen (1962)[189]	Liberia (1963)	• All children in 16 schools in Monrovia aged between 3 and 20 years • Examined malaria by microscopy	1,693 microscopy examinations

Table 1.1 continued

Authors	Country and year of study	Methods	No. examined
Onori & Benthein (1967)[190]	Uganda (Busoga district) (1964 – 1965)	• 3 monthly surveys in 10 schools in Busoga district • Spleen and microscopy examinations in all sampled children	1,168 spleen and microscopy examinations in children between the ages of 5 and 15 years
Onori (1967)[191]	Uganda (Karamoja district) (1965)	• Malaria surveys in 15 schools in the district • Spleen and blood smears in all the children	1,300 spleen and microscopy examinations in children between the ages of 5 and 15 years

Although school-based malaria surveys fell out of use in malaria surveillance, the use of schools has several advantages. First, school-based surveys have been shown to be easier and cheaper to conduct than household-based surveys since location and sampling of children is made easy[46]. Second, school children represent a major proportion of the children in the 2-10 year age group which is epidemiologically ideal for measuring malaria transmission[31]. However, the representativeness of school-based surveys in estimating infection prevalence in school-age children crucially depends on the level of school enrolment and absenteeism due to malaria[46].

In addition, the early school-based malaria surveys commonly used a two stage process: all children examined for splenomegaly and then a selection of children with enlarged spleens selected for blood collection and microscopy. Whilst the use of splenomegaly to define malaria transmission intensity may have limited use in Africa due to the multiple causes of splenomegaly, the two stage process used in the early surveys may still be useful. Recent surveys, such as the MIS, have used RDTs to allow immediate treatment of infections as well as a screening tool for positives that require further investigation with the more accurate diagnostics such as microscopy and PCR. There is need however for comparative studies to assess the costs associated with different diagnostic strategies in school surveys at varying prevalence levels.

As well as estimating infection prevalence, school malaria surveys can be used to estimate intervention coverage among school-age children. However, unlike in the household surveys where the presence or absence of ITNs can be accurately ascertained, the estimates of ITN coverage in school surveys rely on reports from school children. Encouragingly, a study in Uganda found that reports by schoolchildren on household net ownership provide a rapid method to collect reliable coverage data at the community level[192]. The issue of reliability of school children's reports on ITN ownership and use, and congruence with household-based surveys thus warrants further investigation.

1.8. Aims, objectives and thesis outline

1.8.1. Thesis aims and objectives

The two principal aims of this thesis are to (i) evaluate in different transmission settings in Kenya the usefulness of school-based malaria surveillance to define the epidemiology and burden of malaria and (ii) evaluate the impact of school-based approaches to control malaria in different transmission settings in Kenya. These aims will met by exploring the following specific objectives:

1. To describe the epidemiology of malaria among school children in Kenya, using data from a nationwide school survey.
2. To determine the association between reported ITN use, malaria parasitemia and anaemia among school children in different transmission settings in Kenya.
3. To evaluate the impact of LLINs distributed through schools on parasitemia, anaemia and reported net use among school children in a low transmission setting.
4. To determine the reliability of RDTs and the cost implications of using alternative diagnostic methods, including microscopy and PCR for school-based malaria surveillance in different transmission settings
5. To assess the reliability of school children's reports of ITN use as a proxy for monitoring community level coverage of ITNs and for malaria control planning.

1.8.2. Thesis outline

Chapter 2 describes the study design of a series of nationwide schools malaria surveys in Kenya and reports the geographical distribution of *Plasmodium* infection, anaemia and patterns of reported ITN use in Kenyan school children. These data are subsequently used to investigate additional specific objectives. Chapter 3 evaluates the risk factors for

Plasmodium infection and anaemia in the varying malaria transmission zones in Kenya, and quantifies the potential efficacy of ITNs on *Plasmodium* infection and anaemia in these varying malaria ecologies. To further inform the use of ITNs for malaria control in school children in Kenya, chapter 4 describes a cluster randomised trial that evaluates the impact of LLIN distributed through schools on anaemia, *Plasmodium* infection and reported net use among school children in Tana River and Tana Delta districts in Kenya, where malaria transmission is low. To evaluate the usefulness of school malaria surveys for malaria surveillance, Chapter 5 investigates the reliability of RDTs in malaria school-based surveys and evaluates the relative costs and usefulness of RDTs in defining malaria risk compared to alternative diagnostic strategies. Chapter 6, then evaluates the reliability of school children's reports on ITN use and ownership, and further explores the congruence of school-based net use reports with net use estimates from household based surveys for control planning. Finally, chapter 7 discusses the main findings and highlights the important issues that have arisen from this work.

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Chapter 2 : Implementing school malaria surveys in Kenya: towards a national surveillance system

2.1. Overview

Effective targeting of malaria control interventions needs to be based on empirical data on the burden and distribution of disease. As highlighted in Chapter 1, there are limited data on the epidemiology of malaria in school age children for effective control planning. This chapter therefore aims to describe the spatial patterns of *Plasmodium* infection, anaemia and bed net use among school children in Kenya using a series of nationwide school malaria surveys undertaken in Kenya between 2008 and 2010. The study design, the methodological issues encountered in the implementation of the school surveys and their implications on future malaria surveillance in Kenya are discussed.

This chapter has been peer reviewed and published in the *Malaria Journal*: *Gitonga CW, Karanja PN, Kihara J, Mwanje M, Juma E, Snow RW, Noor AM, Brooker SJ, 2010. Implementing school malaria surveys in Kenya: towards a national surveillance system. Malaria Journal 9: 306.* I participated in the design of the survey, with support from my supervisor Professor Simon Brooker and my advisory committee members, Professor Bob Snow and Dr Abdisalan Noor. I also coordinated the fieldwork and undertook all the analysis presented in this chapter.

2.2. Background

The epidemiology of malaria in sub-Saharan Africa (SSA) is in transition, with funding agencies dedicating substantial resources in tackling malaria and national governments making great efforts in increasing access to malaria control interventions. It is essential that this transition is accurately monitored in order to evaluate the impact of interventions but also to allow for better targeting of interventions. A number of studies provide evidence of declining malaria-related mortality and morbidity[1-5], but there is, surprisingly, little evidence of the impact of control on malaria transmission. This is most commonly measured on the basis of the parasite rate (PR), since it is readily measured in the field and provides reliable information on other measures of malaria transmission, including the entomological inoculation rate and basic reproductive number[6].

Consequently, estimates of PR form the best evidence base for planning, implementing and evaluating control, with PR among children aged two to 10 years providing a standard measure of PR[7]. To date, malaria monitoring and evaluation of interventions in malaria endemic countries in SSA has been mainly based on periodic national household surveys, including malaria indicator survey [8] as well as malaria modules of demographic health surveys [9] and multiple indicator cluster surveys[10], where young children and pregnant women form the sample population. The principal advantages of such household surveys are that they adequately capture the underlying variation in the sampled population and the flexibility of data collection instruments which can accommodate a number of questions on a variety of topics. However, household surveys are expensive, time consuming and labour intensive, and generally only undertaken every 3-5 years and therefore not ideal for routine monitoring at local levels. Furthermore, estimates of *Plasmodium* infection collected among young children and pregnant may not be optimal due to the modifying presence of maternal antibodies and sequestered parasites[11]. A cheaper and rapid complementary approach to household surveys would be to use the existing school system for school-based malariometric surveys[11].

Historically, such school surveys were routinely conducted as part of malaria surveillance in Africa[11] and today, school surveys for helminth infections are an essential component of the design and evaluation of helminth control[12, 13]. Learning from these historic and contemporary experiences, this chapter reports the study design and main findings of a series of large-scale school malaria surveys in Kenya, with a view to informing future nationwide school-based surveillance. Particular guidance is provided on the consent for participation, field logistics and implementation of the survey and reflection is made on the ethical, practical and methodological issues encountered in conducting malaria surveys in schools.

2.3. Methods

2.3.1. The Kenyan context

The epidemiology of malaria in Kenya has been changing with reported reductions in malaria associated hospital admissions and mortality in children under the age of five years [14-16]. These changes have been, in part, attributed to the increase in coverage and access to malaria control interventions, such as insecticide-treated nets (ITNs), artemisinin-based combination therapy (ACT) and indoor residual spraying (IRS) [16]. In an effort to scale up ITN coverage, Kenya has adopted several ITN distribution strategies over the years, including social marketing, subsidized nets through the maternal and child clinics, and mass campaigns [16, 17]. Other malaria control efforts include the change of the treatment policy in 2004 and implemented in 2006 to adopt the more efficacious ACT as well as IRS in the epidemic prone districts.

In 2009, the Government of Kenya launched its National Malaria Strategy (NMS), 2009-2017. This identified the need to tailor malaria control interventions to the local diversity of malaria risk, target specific population sub-groups to achieve effective and sustainable control, and strengthen the surveillance, monitoring and evaluation systems [18]. One approach to target population sub-groups includes the control of malaria in schools under a Malaria-free Schools Initiative. These plans for school-based malaria control build on recent success in delivering deworming through schools in Kenya. Implementation of the national deworming programme was guided by school surveys of helminth infection which showed that mass treatment was only warranted in selected regions of the country[19] thereby increasing the efficiency of the programme. Before appropriate suites of malaria intervention can be planned efficiently for the Malaria-free Schools Initiative, equivalent data are required concerning the prevalence and distribution of malaria, anaemia, and intervention coverage across the country.

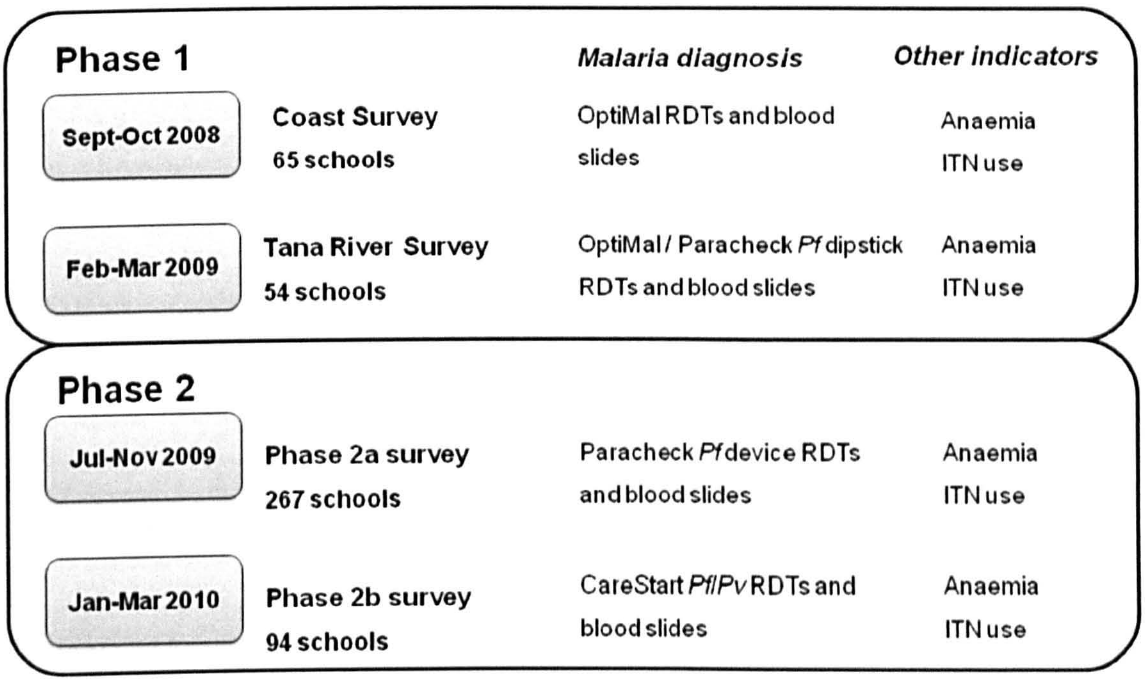
The Kenya NMS also included the proposal to undertake school malaria surveys to monitor trends of malaria transmission in the context of increasing intervention coverage. Such school surveys have a historical precedent in Kenya, dating back to the 1950s, when the Division of Vector Borne Diseases (DVBD) was established and school surveys of malaria, helminths and other parasites were one of its core activities. Routine school survey stopped in the 1980s due to financial constraints and deteriorating school enrolment rates [20].

The renewed potential for school malaria surveys builds on the increased funding for malaria surveillance but also recent improvements in primary school enrolment in Kenya. There are a total of 19,177 government primary schools, the majority (98.5%) of which are day schools with pupils living at home. Primary education in Kenya begins at the age of 6 or 7 years old after completion of a year of nursery school and includes eight years of schooling. The Kenyan school year runs from January to December. In the 1980s and 1990s, there was a growth of privately owned schools while the government schools deteriorated. In 2003, the Government of Kenya re-introduced free primary education, resulting in a marked increase in school enrolment. However, parents must pay fees for uniforms and other items and some poorer children still do not attend primary school. The overall net enrolment rate (NER: ratio of children of official school age who are enrolled in school to the population of the corresponding official school age.) in Kenya was 91.6% in 2007, but this ranged from 27.5% in North Eastern Province to 97.8% in Nyanza Province [21].

2.3.2. Sample design and study population

The surveys were conducted in two principal phases (see Figures 2.1 and 2.2), based on the availability of resources at the time and intended purposes of each phase. The first phase was opportunistic in terms of malaria surveillance and included 65 schools sampled in three contiguous districts (the 1999 districts of Kwale, Kilifi and Malindi) along the Kenyan Coast, September-October 2008, as part of baseline surveys aimed at informing the implementation of the national school deworming programme (Figure 2.2). These surveys sought to define the prevalence of *Plasmodium* infection in a given district based on 95% confidence limits, 80% power, and a design effect of 2. Based on these assumptions, a minimum sample size of 16 schools per district was calculated as necessary to estimate prevalence of 5%, with 1% precision. An additional 54 schools were sampled as part of an evaluation of school net distribution programmes along the Tana River (Figure 2.2). These surveys meant that all districts in Coast Province, except Lamu District, were included in the first phase of the survey.

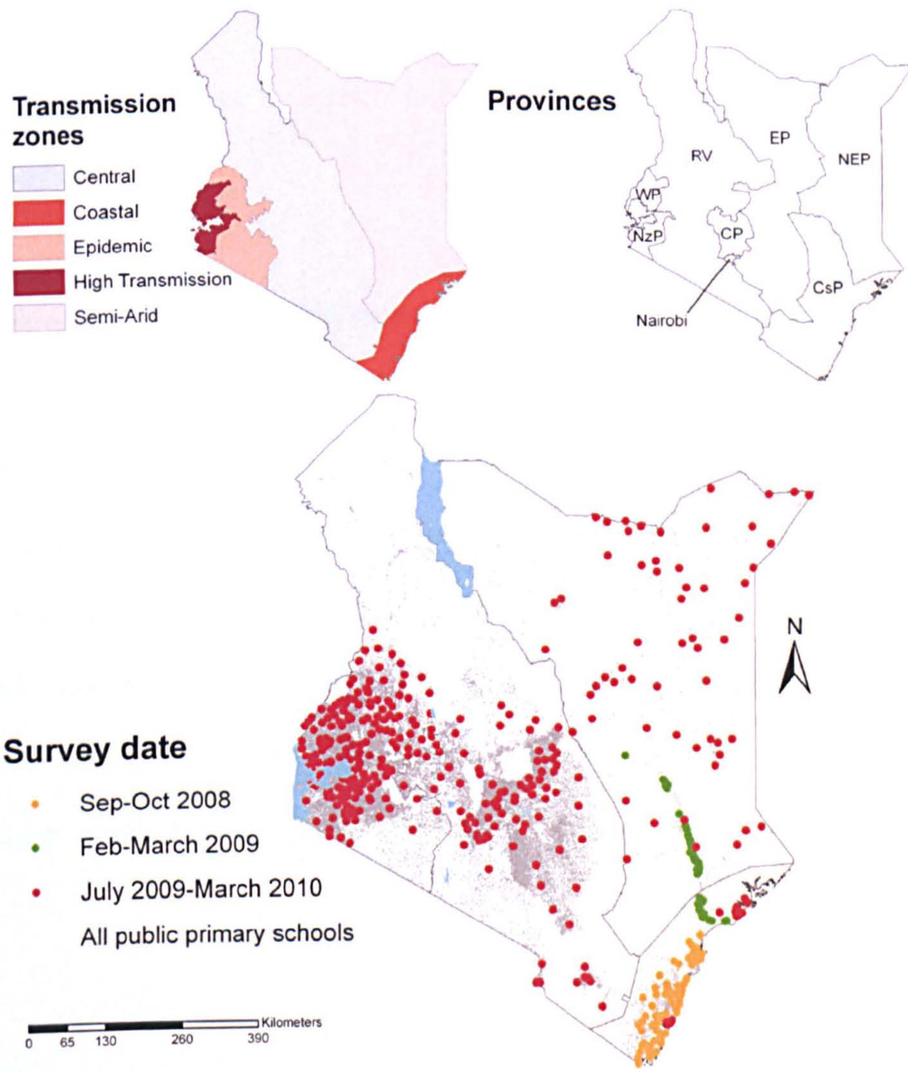
Figure 2.1. Flow chart showing the two principle phases of the school malaria surveys, including timelines, rapid diagnostic test type and other indication data collected.



Based on these initial surveys, the second phase sought to create a nationwide sample of schools to allow for adequate spatial representation of malaria across the country, rather than provide precise estimation of prevalence at national and sub-national levels. Schools were selected from all remaining districts across the country with the exception of semi-arid districts in northern and southern Rift Valley Province (Figure 2.2).

The sampling frame for this selection was the national schools census undertaken by the Ministry of Education (MoE) in 2008 of primary, secondary, public and private schools nationwide (MoE, 2008). For the purposes of the present survey, only public, mixed primary schools were selected as the universe of sampling, totalling 19,177. From this universe, approximately five schools in each of 70 district boundaries used during the 1999 census were selected.

Figure 2.2. The geographical distribution of the 480 sampled schools according to study phase. These schools are overlaid on the distribution of all the 19,177 government, mixed primary schools in Kenya (Kenya Ministry of Education, 2008). Insert: Malaria transmission zones in Kenya based on a geostatistical model of *Plasmodium* prevalence[22] and the different level 1 administrative regions (Provinces: NzP =Nyanza Province, WP = Western Province; RV = Rift Valley Province; EP = Eastern Province; NEP = North Eastern Province; CP = Central Province; CsP = Coast Province).



The selection of schools in each district was not weighted by population or fully random since schools were selected to provide adequate spatial spread of school locations, a requirement of geostatistical modelling of risk across space and time[23]. Finally, two over-sampling adjustments were undertaken: schools were over-sampled, disproportionate to district weighted school distributions, in the sparsely populated areas of North Eastern Province to increase the power of spatial interpolation of risk in these areas; and second, schools were purposively over-sampled in Central Kisii, Gucha and Rachuonyo districts where indoor residual spraying programmes were rolled out in 2008 to investigate impacts with time in these areas. A total of 361 schools were surveyed in the second phase during the second and third term of the 2009-2010 school year (June-November, 2009) and the first term (January-March, 2010) (Figure 2.2). The final sample included 480 schools sampled for malaria infection prevalence between September 2008 and March 2010.

Taking into account a combination of sample precision, logistics and costs, it was decided that a randomly selected sample of 100 children (plus 10 reserves) per school would be optimal as this was the number of children, which could practically be sampled in a single day. In each school, 11 boys and 11 girls were selected from each of classes 2-6 using computer generated random table numbers. If there were insufficient pupils in these classes, additional pupils were sampled from class 1. Some of the schools visited were small, and this meant that in these schools all children were selected to achieve the target sample size and fewer than 110 children were present and, therefore, examined.

2.3.3. Team composition and logistics

Mobile survey teams consisted of a team leader, three laboratory technicians and three interviewers. Technicians were typically from the Division of Vector Borne and Neglected Tropical Diseases (DVBNTD) of Ministry of Public Health and Sanitation, holding diplomas or first degrees and who had extensive experience of conducting school surveys. Interviewers were either from the Ministry of Public Health and Sanitation or Ministry of Education, who had previous survey experience. Each team was supervised from an experienced researcher from the Kenyan Medical Research Institute (KEMRI) or KEMRI-Wellcome Trust Research Programme. These teams were accompanied by an education officer from the district education office who helped teams locate schools.

All team members underwent training in all survey procedures and received a field manual outlining the survey purpose and methods. Data collection occurred during the course of a school term, with each team travelling in a single vehicle with supplies necessary for a single term. An exception was heat sensitive supplies, such as malaria rapid diagnostic tests (RDTs) and haemoglobin microcuvettes, which were sent to teams on a weekly or fortnightly basis. Teams sent back blood slides and filter papers to Nairobi weekly in appropriate storage.

2.3.4. Community sensitization

This took place at national, provincial and district levels before visiting the schools, using a cascade approach. At the national levels, the study was approved by the Division of Malaria Control, Ministry of Public Health and Sanitation and the Director of Basic Education, Ministry of Education. Supporting letters from these ministries were sent to provincial health and education officers, detailing the purpose of the survey, survey timetable and procedures. Upon arriving in a province, meetings were held with the Provincial Medical Officers and the Provincial Directors of Education. These offices provided further letters of support to relevant district authorities and in each district, meetings were held with relevant district health and education officials.

2.3.5. Surveys procedures

Selected children were asked to provide a finger-prick blood sample, which was used to assess *Plasmodium* infection in the peripheral blood and haemoglobin concentration. Children had both a RDT, which gave an on-the-spot diagnosis, and provided thick and thin blood films for microscopy. The RDT used differed according to survey phase (see Figure 2.1 and Table 2.1). The majority of children were tested with either a ParaCheck-*Pf* device or a ParaCheck-*Pf* dipstick[24], these tests are able to detect *P. falciparum*. During the September-October 2008 surveys on the coast, the RDT used was OptiMAL-IT [25] able to detect *P. falciparum* and other, non-falciparum plasmodia species. For surveys conducted in January-March 2010, the main RDT used was CareStart Malaria Pf/Pv Combo [26] which can detect both *P. falciparum* and *P. vivax*. Prior to use, RDTs were stored at room temperature and transported to the school in a cooler box and the desiccant in the RDTs was inspected for colour changes before use, and the RDT discarded if the colour had changed. Children with positive RDTs and documented fever were provided with artemether-lumefantrine (Coartem, Novartis, artemether 20 mg/lumefantrine 120 mg) according to national guidelines.

In all 480 schools, thick and thin blood smears were also prepared for each child. Slides were labelled and air-dried horizontally in a carrying case in the field, and stained with 3% Giemsa for 45 minutes at the nearest health facility when the teams returned from the school. Due to supply difficulties in securing Hemocue curvettes for all schools, haemoglobin concentration was assessed in 399 schools and estimated to an accuracy of 1 g/L using a portable haemoglobinometer (Hemocue Ltd, Angelhölm, Sweden). Children identified as severely anaemic (haemoglobin levels < 70 g/L) were referred to the nearest health facility for treatment according to national guidelines. Transportation costs were provided and an agreement was reached with facilities to waive drug costs.

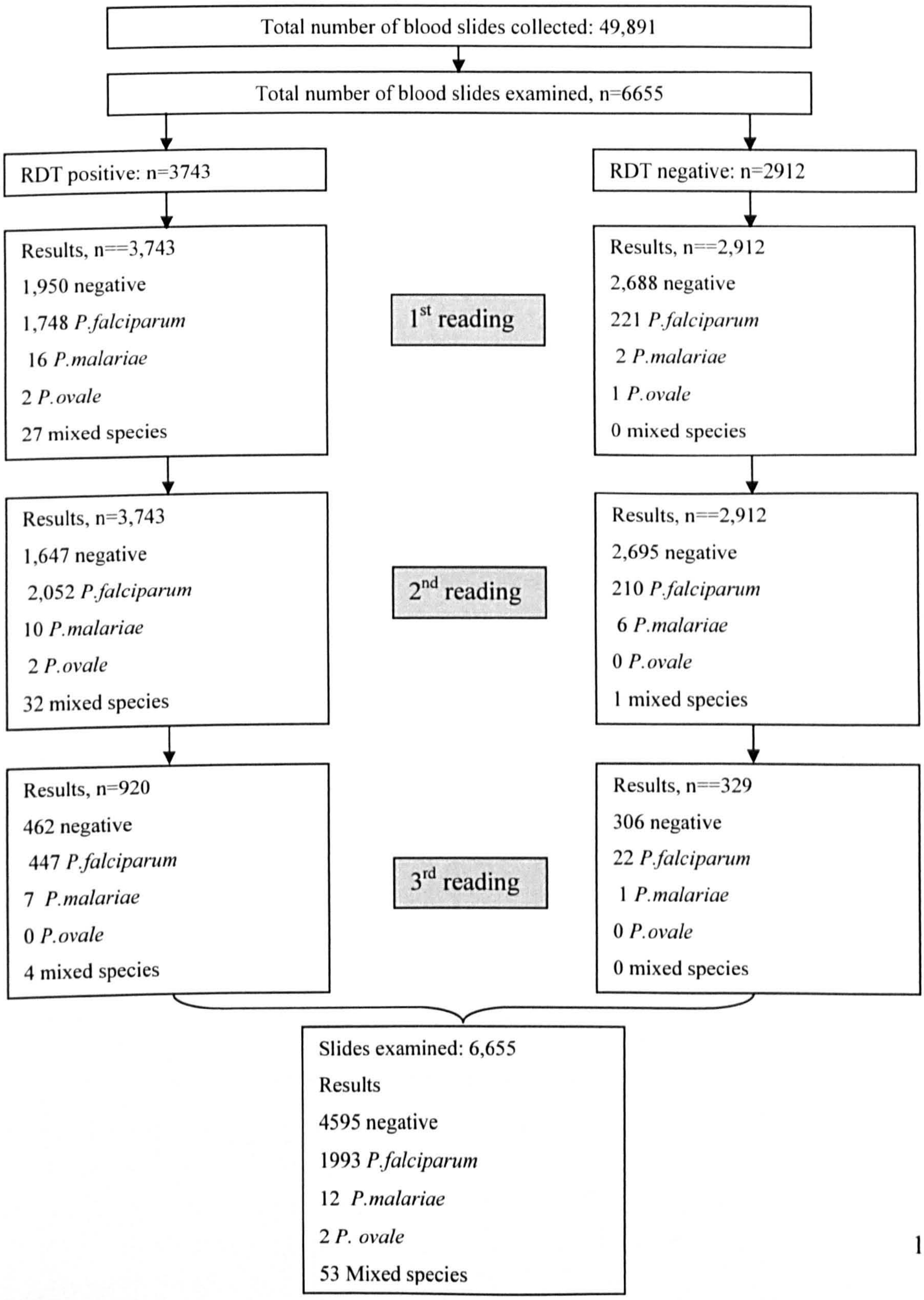
A questionnaire was administered to pupils to obtain data on mosquito net ownership and use and when treated, recent travel history, recent history of illness, key socio-economic variables such as household construction, education level of the child's guardian and ownership of household items such as mobile phones. An additional questionnaire was administered to the head teacher to collect information on ongoing school health activities, including malaria control, as well as information, education and communication (IEC) material on malaria. The pupil and school questionnaire data will be used in future analyses. The geographical location of each school was determined using a Garmin eTrex global positioning system [27].

2.3.6. Expert microscopy

Blood smears of all RDT-positive children, where available, and an equivalent number of randomly selected blood slides from RDT-negative children were examined by expert microscopy either at the KEMRI/Wellcome Trust laboratory in Kilifi or the KEMRI laboratory in Nairobi. Parasite densities were determined from thick blood smears by counting the number of asexual parasites per 200 white blood cells (or per 500 if the count was less than 10 parasites/200 white cells), assuming a white blood cell count of 8,000/μl. A smear was considered negative after reviewing 100 high-powered fields.

Thin blood smears were reviewed for species identification. Two independent microscopists read the slides, with a third microscopist resolving discrepant results (see Figure 2.3 for microscopy results flowchart).

Figure 2.3. Microscopy results flowchart



Of the 6,655 slides examined, the overall sensitivity and specificity of the RDTs was 96.1% (95% CI: 95.2-96.9) and 61.6% (95% CI: 60.2-63.0). Diagnostic performance was similar for three types, but very poor for CareStart: 94.9% sensitivity and 77.4% specificity for OptiMal; 96.2% sensitivity and 68.7% specificity for Paracheck device; 96.3% sensitivity and 76.0% specificity for Paracheck dipstick; and 100% sensitivity and 2.0% specificity for CareStart. In light of the poor performance of CareStart, we only present slide-corrected RDT results. A more detailed investigation of the reliability of RDTs in the context of school-based malaria surveillance is presented in Chapter 5.

2.3.7. Electronic data capture

Children's responses were entered electronically in the school on either ASUS Eee PC 1005P or Acer Aspire One d250 netbook computers using a customized Microsoft Access database, which included in-built checks to prevent some errors altogether and immediately prompting for resolution of other errors. Computers were powered by batteries, backed up by solar panels or small diesel generators. At the end of each day, interview data were combined with parasitological data and transmitted nightly to Nairobi using a mobile phone modem connection. In some parts of northern Kenya, delays of 1- 2 days were experienced in transmitting the data due to poor network coverage.

2.3.8. Data analysis

Data were analyzed using STATA version 11.0 (STATA Corporation, College Station, TX, USA). The locations of schools were linked with survey data and mapped using Arc GIS 9.2 (ESRI, Redlands, CA, USA).

Anaemia was defined as a haemoglobin concentration <130g/L for male children above 15 years, <120 g/L for children aged 12-14 years and female children above 15 years, <115 g/L for children aged 5-11 years and <110 g/L for children aged less than five years, with adjustment made for altitude of the school [28]. Severe anaemia was defined as a haemoglobin level <70g/L.

Results were adjusted for clustering at the school-level using random effects regression modelling [29]. Specifically, national- and province-level estimates of *Plasmodium* infection and corresponding 95% binomial confidence intervals (CI) were estimated using a zero inflated Poisson (ZIP) model to account for the excess of schools with zero prevalence. The ZIP model was favoured over a standard Poisson model on the basis of the Vuong test [30]. The ZIP model was used for all the provincial level estimates of *Plasmodium* infection except for Nairobi and Rift Valley provinces where a standard Poisson model was used. National and Province-level estimates of anaemia and net use were estimated using generalized linear and latent mixed models (GLLAMM) adjusted for clustering at the school level.

The overall financial cost of the survey was estimated from the project accounting system, with costs divided into staff, transport, operating costs and consumables.

2.3.9. Ethical considerations

The study protocol received ethical approval from the Kenya Medical Research Institute and National Ethics Review Committee (numbers 1407 and 1596). Additional approval was provided by the Permanent Secretary's office of the Ministry of Education (MoE) and the Division of Malaria Control, Ministry of Public Health and Sanitation. All national, provincial and district-level health and education authorities were briefed about the survey purpose and selected schools. Official letters of support were prepared by Provincial MoE officers.

Head teachers were briefed about the survey and were provided with an information sheet detailing the survey procedures and asking for their permission to have their school involved in the survey. The head teachers were also asked to inform the students, parents and the school committee members about the survey and obtain their approval for the study. Parents/guardians who did not want their children to participate in the study were free to refuse participation. If a parent or guardian chose not to allow their children to participate in the survey, the child's name was removed from the school rolls. On the survey day, the survey team leader informed all children in the school about the sampling and survey procedures, making it clear to their participation was voluntary and that they may opt out of the testing at any time if they choose to. After randomly sampling the students from the classrooms, individual assent was also obtained from the children before samples were collected. Very few children refused to participate in the survey and therefore replacement sampling was not required. Individual written parental consent was not sought since the survey was conducted under the auspices of the Division of Malaria Control, Ministry of Public Health and Sanitation, which has the legal mandate to conduct routine malaria surveillance, and because only routine diagnostic procedures were undertaken.

2.4. Results

2.4.1. Survey process

The surveys were carried out in two main phases (Figure 2.2 and Table 2.1): first, two independent surveys, September 2008 to March 2009; and second, a purposively selected sample of 361 schools, June 2009 to February 2010. Up to five separate teams were in the field at any one time, including up to 24 laboratory technicians. These were either recruited locally in each province from the Ministry of Public Health and Sanitation's Division of Vector Borne and Neglected Tropical Diseases, or recruited in Nairobi from KEMRI's Eastern and Southern Africa Centre of International Parasite Control (KEMRI/ESACIPAC). The majority technicians had prior experience of carrying out school surveys. Mobile telephone coverage was available throughout most of Kenya, enabling sending of data to Nairobi on a daily basis.

The average cost of surveying one school was estimated to be US$ 1,116. The largest cost component was staff (32.0%), following by transport (26.9%). Operating costs included laboratory consumables, courier services and hiring of mini-laptop computers and accounted for 24.7% of total costs. Other costs included slide reading (7.2%) and administration costs (9.2%).

2.4.2. Characteristics of study participants

A total of 49,975 children in 480 schools across Kenya were included in the survey. Table 2.1 presents the characteristics of the study children and their schools. In each school, an average of 103 (range 23 – 115) children was selected, with an equivalent number of boys and girls sampled (51.3% boys). The median age was 11 years (inter-quartile range: 10-13 years) and most children (67.3%) were in the 10 to 15 age group. The majority (74.8%) of schools were surveyed during the second phase of the surveys, June 2009-March 2010. Data on malaria infection and ITN use were collected in all schools, whereas haemoglobin concentration was assessed in 399 schools.

Table 2.1. The number of schools and number of school children by study phase, malaria transmission zone, age group, sex, malaria rapid diagnostic test (RDT) used, included in school malaria surveys in Kenya, 2008-2010.

	Schools	N children (%)
Study phase		
Sept-Oct 2008	65	6,884 (13.8)
Feb-March 2009	54	5,694 (11.4)
June 2009-March 2010	361	37,397 (74.8)
Malaria transmission zone		
High transmission lakeside	80	8,186 (16.4)
Western highland epidemic	100	10,819 (21.7)
Coast moderate risk	95	10,172 (20.4)
Central low risk	110	11,275 (22.6)
North eastern semi arid	95	9,523 (19.1)
Age group		
5-9 years		12,338 (24.7)
10-15 years		33,650 (67.3)
>15 years		3,763 (7.5)
Missing[1]		224 (0.5)
Sex		
Male		25,656 (51.3)
Female		24,217 (48.5)
Missing[1]		102 (0.2)
RDT test		
CareStart Malaria Pf/Pv Combo	96	9,064 (18.2)
OptiMAL-IT	71	7,801 (15.6)
ParaCheck device	246	26,326 (52.8)
ParaCheck dipstick	67	6,700 (13.4)

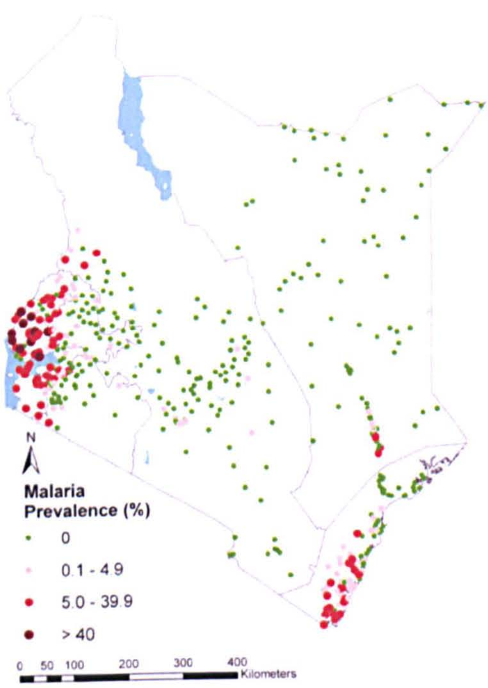
[1] Data was not recorded

2.4.3. Malaria infection

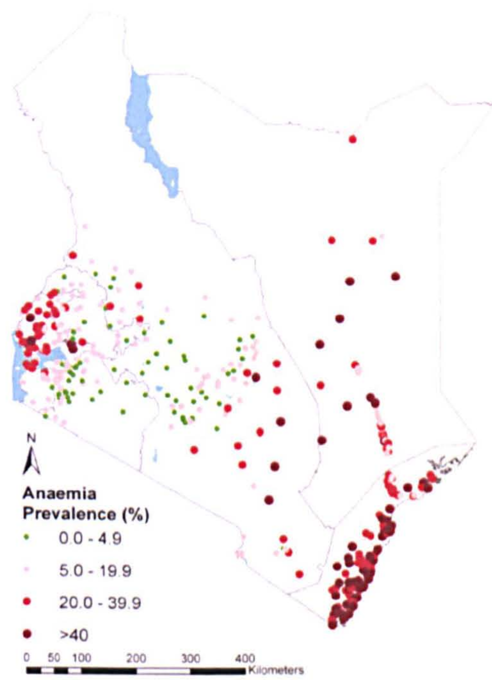
The overall prevalence of infection, based on slide-corrected RDT positivity, was 4.3 (95% CI, 3.3 – 5.2).The vast majority (96.8%) of these infections were *P. falciparum*, with the remainder being either *P. ovale* (0.1%) or *P. malariae* (0.6%) or mixed infections (2.6%); no *P. vivax* was detected. Prevalence was significantly higher in children aged 5-9 and 10-14 years old (4.4%) than children older than 15 years (2.8%, p<0.0001), but did not significantly differ between males and females (4.3% vs. 4.2%, p=0.53). The prevalence of malaria infection by province is shown in Table 2.2 and the geographical distribution of malaria is shown in Figure 2.4a. Prevalence varied markedly by school (0 – 70.9%) and by province, being highest in Western Province (21.6 %, 95% CI: 14.6 – 28.7%) and lowest in Central and North Eastern provinces, where no child was found to be infected in any school (Table 2.2). Prevalence was <5% in all other provinces, except Nyanza Province (9.3%, 95% CI: 6.8 – 11.9%). Eleven (2.3 %) schools had a parasite prevalence ≥ 40% and all of these were located around Lake Victoria (Figure 2.4a).

Figure 2.4. The geographical distribution of (a) Malaria infection based on microscopy-corrected RDT results in 480 schools, (b) anaemia adjusted for age, sex and altitude in 399 schools, and (c) report insecticide net use among school children in 480 schools across Kenya, September 2008-March 2010. Note: Haemoglobin was not assessed in some schools in the North Eastern Kenya. Classification based on the WHO categories of anaemia for public health importance[28].

(a)



(b)



(c)

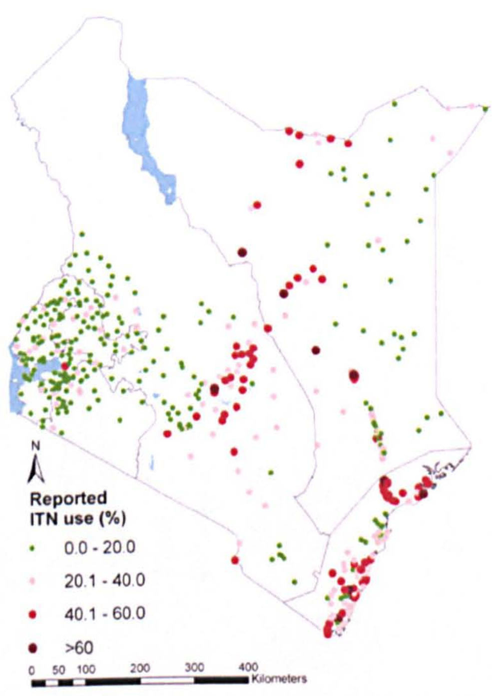


Table 2.2. The prevalence of malaria infection based on RDTs alone and blood slide corrected RDT results in primary school children by province in Kenya, 2008 – 2010.

				***Plasmodium* spp.**			
	N[1]	**Prevalence by RDTs (%, 95% CI)[2]**	**Prevalence: slide corrected (%, 95% CI)[3]**	**Slide corrected prevalence category (n, %)**			
				0%	**0.1-4.9%**	**5-39.9%**	**≥40%**
Total	480 / 49,891	7.6 (6.4 – 8.9)	4.3 (3.3 – 5.2)	296 (1.7)	98 (20.4)	75 (15.6)	11 (2.3)
Province							
Nyanza	90 / 9,299	19.6 (16.0 – 23.1)	9.3 (6.8 – 11.9)	30 (33.3)	25 (27.8)	31 (34.4)	4 (4.4)
Western	37 / 3,892	32.4 (25.2 – 39.6)	21.6 (14.6 – 28.7)	5 (13.5)	8 (21.6)	17 (45.9)	7 (18.9)
Central	22 / 2,387	0	0	22 (100)	0	0	0
Rift Valley	87 / 9,202	1.2 (0.7 – 2.0)	0.8 (0.4 – 1.5)	66 (75.9)	16 (18.4)	5 (5.7)	0
Nairobi	10 / 917	1.9 (1.2 – 3.0)	1.1 (0.6 – 1.6)	3 (30.0)	7 (70.0)	0	0
Eastern	52 / 5,355	0.2 (0.1 – 0.4)	0.1 (0.0 – 0.2)	49 (94.2)	3 (5.8)	0	0
North Eastern	43 / 4,087	1.0 (0.5 – 1.5)	0	43 (100)	0	0	0
Coast	139 / 14,752	3.8 (2.9 – 4.6)	2.3 (1.7 – 2.9)	78 (56.1)	39 (28.1)	22 (15.8)	0

[1] Number of schools surveyed / children tested, excluding schools without microscopy results.
[2] Prevalence and 95% binomial confidence (CI) intervals were calculated using a zero inflated Poisson model adjusted for clustering at the school level, except in Nairobi, Rift Valley and Eastern provinces where a random effects cluster adjusted Poisson model was used.
[3] Prevalence and 95% binomial confidence (CI) intervals were calculated using a zero inflated Poisson model adjusted for clustering at the school level, except in Nairobi and Rift Valley provinces where a random effects Poisson model was used.

2.4.4. Anaemia

The overall prevalence of anaemia was 14.1% (95% CI: 13.0–15.3%) and the mean haemoglobin concentration was 128.8 g/L (95% CI: 127.9–129.7 g/L). Anaemia was more common among children aged 15 years and above (38.6%, 95% CI: 33.1–44.9%) than 10-14 years (14.9%, 95% CI: 12.6–17.5%) and 5-9 year olds (14.0%, 95% CI: 14.1–18.1%). There was no difference in prevalence of anaemia among males and females (13.3% (95% CI: 12.1-14.7) vs 13.3 (95%CI: 12.0-14.8)). Anaemia varied markedly by school (0-75%, figure 2.4b) and was more common in Coast Province and least common in Central Province (Table 2.3).

2.4.5. Reported ITN use

Overall, 44.2% (95% CI: 42.7-45.6%) of children reported having a bed net and 42.1% (95% CI: 40.9-42.8%) reported sleeping under a net the previous night. However, of the children asked about sleeping under an ITN, less than a quarter (19.0%, 95% CI: 18.0–20.2%) reported sleeping under an ITN while 6.4% did not know whether their nets were ITNs or not. The majority (70.9%, 95% CI: 68.6–73.2%) of nets, non-ITNs or ITNs, were reportedly obtained from the health facilities. Reported use of ITNs varied markedly across the country (Figure 2.4c), and was <20% in the majority (55.0%) of schools, especially in Nyanza and Western Provinces; disappointedly, only eleven schools had reported ITN use >60% (Table 2.3). In terms of household net ownership, 80.3% of children reported having at least one bed net in their household while 77.1% reported more than one net in their households. Nyanza Province had the highest number of children reporting having at least one net in their household (88.9%) while Central Province had the lowest (57.1%).

Table 2.3. The prevalence of anaemia and the proportion of school children reporting using and sleeping under a long-lasting insecticide net the previous night by province in Kenya, 2008-2010.

	Anaemia		**Reported any net**			**Reported insecticide-treated net use**		
	N[1]	**Prevalence (%, 95% CI)[2]**	**N[1]**	**Ownership (%, 95 % CI)[2]**	**Reported use (%, 95% CI)[2]**	**Schools with <20% use, (n, %)**	**Schools with ≥60% use, (n, %)**	**Overall use (%, 95% CI)[2]**
Total	399 / 41,920	14.1 (13.0-15.3)	480 / 49,797	44.2 (42.7-45.6)	42.1 (40.9-42.8)	264 (55.0)	11 (2.3)	19.0 (18.0-20.2)
Province								
Nyanza	85 / 8,969	11.3 (9.6-13.3)	90 / 9,316	39.9 (38.2-41.5)	38.5 (36.8-40.1)	73 (81.1)	0	13.5 (12.1-15.0)
Western	35 / 3,751	19.8 (15.7-25.1)	37 / 3,892	44.1 (42.1-46.0)	41.1 (38.0-44.2)	30 (81.1)	0	13.3 (11.2-15.6)
Central	22 / 2,387	3.6 (2.3 -5.4)	22 / 2,387	37.8 (36.2-39.5)	37.1 (35.4-38.7)	14 (63.6)	2 (9.1)	10.8 (8.6-13.5)
Rift Valley	63 / 6,629	6.8 (5.5-8.3)	90 / 9,202	29.7 (27.7-31.7)	28.7 (27.0-30.4)	71 (78.9)	0	9.5 (8.2-11.1)
Nairobi	10 / 924	5.2 (3.7-7.4)	10 / 919	44.7 (41.4-48.1)	38.6 (34.8-42.5)	8 (80.0)	0	17.3 (12.3-24.6)
Eastern	33 / 3,399	12.4 (9.8-15.5)	52 / 5,355	69.4 (67.1-71.7)	55.2 (52.8-57.5)	5 (9.6)	2 (3.8)	40.0 (36.9-43.4)
North Eastern	13 / 1,262	32.8 (26.7-40.4)	43 / 4,078	60.1 (57.9-62.2)	50.5 (48.0-53.0)	32 (74.4)	2 (4.7)	4.1 (3.1-5.4)
Coast	138 / 14,599	44.6 (39.8-49.9)	139 / 14,648	66.7 (65.1-68.4)	62.6 (60.5-64.7)	31 (22.3)	5 (3.6)	35.5 (33.0-38.1)

[1] Number of schools surveyed / children tested.
[2] Prevalence and 95% binomial confidence intervals calculated using generalized linear and latent mixed models (GLLAMM) adjusted for clustering at the school level.

2.4.6. Fever and absenteeism

Overall, 13.5% of children reported a fever on the day of the survey, but of the children that had their axillary temperature measured only 733 (2.4%) children had a temperature >37.5 °C. Of these febrile children, only 55 (7.5%) children had a malaria infection. Of the children asked about their absenteeism history (n=37,288), 26.9% of children reported being absent from school due to illness for at least one day in the last two weeks, with the commonest cause of illness being headache (56.7%), whilst 17.0% reported malaria as the cause for absenteeism.

2.4.7. Malaria control activities

A comprehensive school level questionnaire was administered in 344 schools, predominantly in Western, Central, Rift Valley and Nyanza provinces during the second phase of the survey. Of these schools, only 59 (17.2%) reported having had any malaria control activities, such as indoor residual spraying of the school buildings and draining of stagnant water, in the last 12 months and the majority (21) of these schools were located in the malaria high transmission zone. Only, seven schools had malaria IEC materials in at least 1 classroom, 8 had IEC materials in the head teacher's office while 17 schools had IEC booklets in the school library.

2.5. Discussion

Reliable, contemporary data are essential prerequisites for the planning and implementation of effective malaria control. Each national programme needs to be tailored to its specific national context, based on a cartographic understanding of malaria transmission intensity and current intervention coverage. The data from the present study show that although the national prevalence of *Plasmodium* infection was relatively low at 4.3%, there existed marked variation across the country. This finding is consistent with national level malaria prevalence estimate observed in the Kenya MIS in 2007, where the malaria prevalence by RDTs was 7.6% and 3.4% by microscopy [31].

The observed distribution of low transmission in most of Nairobi and Central provinces and some parts of the Eastern and Rift Valley provinces and high transmission along the shores of Lake Victoria and the south coast is consistent with a recent model of malaria risk in Kenya [22]. The current findings also highlight marked variation in the levels of reported ITN use, with levels highest in Eastern and Coast provinces, but surprisingly low reported levels in western Kenya. Interestingly, this low coverage in western Kenya contrasts findings from recent nationwide household cluster surveys among all ages carried out between 2007 and 2009, which showed that ITN/LLIN coverage was similarly high in the western, coastal and central regions of the country [32]. This suggests that in western Kenya, although overall coverage in the community is high, school children are not using ITNs. Possible reasons for the low ITN use among school children have been discussed elsewhere [33, 34], but are likely to reflect a previous focus of net distribution programmes on providing nets to young children and pregnant women. An additional explanation may lie in household sleeping patterns with school children sleeping separately from their younger siblings and parents in areas, such as kitchens, where nets cannot readily be hung [35].

The current survey took advantage of the existing school infrastructure and historical experience in carrying out school surveys in Kenya to achieve a rapid, inexpensive approach to malaria surveillance. The adopted approach has a number of advantages over malaria indicator surveys (MIS) which provide nationally-representative household survey data on coverage of malaria interventions as well as malaria parasitaemia and anaemia among household members most at risk, namely children under five years and pregnant women [8]. First, school surveys make use of an annually updated national school database as a sampling frame, rather than a list of Enumeration Areas (EAs) or clusters from population censes which are typically conducted every 10 years. Second, sampling of children in schools is greatly simplified as children are easily identified from the school register. Third, estimates of parasite rate among school-aged children can be more readily age-standardised to the optimal 2-10 years estimate of *Pf*PR than estimates among under fives and pregnant women [11]. Finally, the costs are greatly reduced: the average cost of surveying one school was estimated to be US$ 1,116. These costs compares to an estimated cost of US$ 3,299 cluster sampled in the Kenya 2007 MIS (Division of Malaria Control, Nairobi, Kenya. Personal communication); however, these estimates represent only financial costs and a detailed economic cost analysis of alternative survey approaches is clearly warranted.

School malaria surveys are not without their limitations, however (for a review see [11]), and a number are highlighted here. First, the representativeness of school surveys will depend on the level of school enrolment. In Kenya, net enrolment rates are lowest in North Eastern Province (27.5%), Nairobi (44.9%) and Coast Province (71.8%) and, therefore, school surveys may not provide a truly representative picture of malaria among school-aged children in these provinces. In the remaining provinces, however, net enrolment rates exceed 90%, increasing the representativeness of school surveys. A further way in which school surveys may be unrepresentative is that children found to be absent on the day of the survey, and therefore not included in the sample population, may be absent due to illness, including malaria. In the current surveys, 26.9% of children reported being absent for at least a day in the two weeks preceding the survey. Due to logistical constraints, no effort was made to follow-up absent children, thus introducing potential selection bias. This may be a particular problem in areas of low malaria transmission, where infection generally leads to clinical disease; whereas in high transmission areas, the majority of infections will be asymptomatic with many of infected children present in school. This issue of potential sampling bias and how it varies according to malaria endemicity deserves further investigation. However, if school surveys underestimate true prevalence of infection in the wider community by a consistent amount, which can be calibrated, schools may still provide a promising platform for malaria surveillance.

A further drawback of school surveys is that they cannot provide complete information on household ownership of insecticide-treated mosquito nets and their use by children under five years of age and pregnant women, or on the use of the intermittent preventive treatment during pregnancy and the type and timing of treatment of fever in children under five years of age. However, a study in Uganda found that reports by schoolchildren on household net ownership provide a rapid method to collect reliable coverage data at the community level [36].

There are also several practical features of the present survey worth highlighting. First, the survey used modern technology to achieve a more cost efficient approach to data collection. In particular, data captured were achieved using netbook computers with customized data entry screens. Electronic data capture systems, mainly based on the use of personal digital assistants (PDAs), are shown to be acceptable and reduce data entry errors considerably [37-40]. Experience in the use of laptops or netbook computers is more limited, but a recent study comparing PDAs and laptops for data capture found the use of laptops was associated with fewer typing errors and missing data [41]. Further use of laptops or netbook computers for data capture in settings where tables can be found, such as schools and health centres, is strongly encouraged.

Second, consent for the survey was based on a passive, opt-out method of parental permission. This approach is considered to be an ethical and practical way of informing participants in low-risk studies and interventions [42], and has been used in a number of school-based studies, including studies in the United Kingdom, United States and India [43-46]. Such consent procedures, when compared to the opt-in methods of seeking parental consent, reduce the time needed to seek consent and maximize participation therefore avoiding significant sampling bias and under-reporting.

Third, malaria parasitaemia was ascertained using a two-stage approach of malaria RDTs and blood slides. Importantly, this approach enabled appropriate treatment of clinical malaria in schools on the day of the survey, but also allowed assessment of the reliability of RDTs at a later stage. A drawback of using RDTs is that they can result in false positives, especially those RDTs that detect the histidine-rich protein-2 (HRP-2) antigen [47-49], leading to an overestimation of infection prevalence [50]. Such overestimation of prevalence using RDTs may lead to misclassification of schools in low and moderately high prevalence, however the effect of such systematic misclassification on resource allocation for malaria control remains unclear and will be the subject of further work.

Encouragingly however the observed sensitivity of RDT in the present study exceeded 90% and are consistent with findings of a recent WHO-FIND evaluation [48].

This chapter has described recent experiences of school malaria surveys in Kenya and highlights the potential of school surveys as a complementary approach for malaria surveillance to the MIS. The findings also highlight the burden of malaria among school children and the marked geographical variation in infection and anaemia as well as in bed net use. The next chapter will further analyse these data to investigate the geographical variation in the associations between infection, anaemia and net use and will discuss their implications for the design of school-based control programmes. Subsequent chapters will investigate the reliability of RDTs in school-based malaria surveys and the reliability of school children's reports of ITN ownership and use. It is hoped that addressing these issues will provide clearer direction on the role, in Kenya and elsewhere, of schools in an integrated national malaria surveillance system, which also includes household surveys and health facility reporting.

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Chapter 3 : *Plasmodium* infection, anaemia and mosquito net use among school children across different settings in Kenya

3.1. Overview

In Chapter 2, I presented results from a nationwide school malaria survey and demonstrated a considerable burden of *Plasmodium* infection and anaemia among Kenyan school children. I also highlighted the marked variation in the prevalence of *Plasmodium* infection and anaemia and in bed net use across Kenya. Such heterogeneity in *Plasmodium* infection is likely to influence the potential efficacy of malaria control interventions such as insecticide treated nets (ITNs) on reducing malaria and anaemia. In turn, geographical differences in observed associations between infection, anaemia and net use should guide the design of an optimal package of school-based malaria control interventions. Using the data presented in Chapter 2, this chapter investigates how the associations between reported net use, malaria parasitaemia and anaemia vary according to age and sex in the different malaria ecologies in Kenya.

This chapter has been published in *Tropical Medicine and International Health*: *Gitonga CW, Edwards T, Karanja PN, Noor AM, Snow RW, Brooker SJ, 2012. Plasmodium infection, anaemia and mosquito net use among school children across different settings in Kenya. Tropical Medicine and International Health 17: 858-70.* I oversaw data collection and was responsible for analysing the data presented in this chapter.

3.2. Introduction

Insecticide-treated nets (ITNs), and more recently long lasting insecticide nets (LLINs), are a key tool in the control of malaria, with demonstrable health benefits of ITN use, especially among young children and pregnant women [1,2]. The age group least likely to use ITNs are school-aged children [3] and few data exist on patterns of net use and effectiveness of nets among this age group [4-6]. In the absence of data from intervention studies, cross-sectional surveys can provide insight on the potential efficacy of ITNs. Survey data from Somalia [7] and Uganda [8] found that school-aged children who reported sleeping under a net the previous night was associated with a 71% and 43% lower risk of *Plasmodium* infection. However, the potential protective efficacy of ITNs in reducing *Plasmodium* infection and anaemia among school children may not be equivalent in all settings due to differences in the underlying intensity of malaria transmission and the relative contribution of other factors that contribute to anaemia among this age group, including undernutrition [9] and helminth infections [10-12].

This chapter investigates putative risk factors, including reported net use, for *Plasmodium* infection and anaemia among school children in Kenya and explore how they vary across the different malaria ecologies that occur in the country. The analysis utilizes data from a recent nationwide school malaria survey in Kenya [13] and examines how the associations between reported net use, malaria parasitaemia and anaemia vary according to age and sex in the different malaria transmission settings.

3.3. Methods

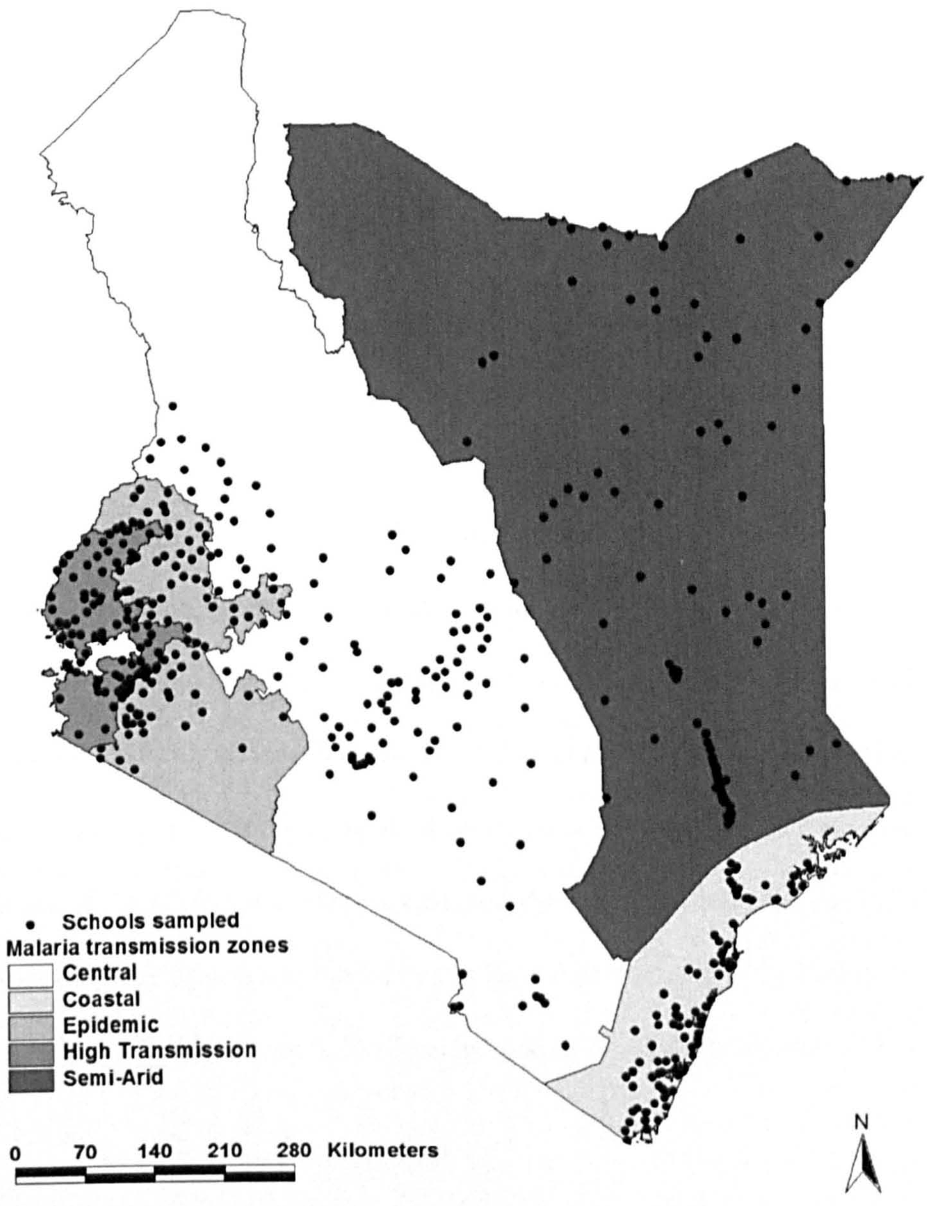
The survey design and procedures of the national survey conducted in 480 schools are detailed in Chapter 2 [13]. In brief, the surveys were conducted in two phases: the first survey phase involved 119 schools in coastal and northeastern Kenya conducted between September 2008 and March 2009; the second survey phase included a sample of schools selected to allow for adequate spatial representation across the country (Figure 3.1), conducted May 2009-March 2010. The selection of pupils in each school was the same for each survey phase: 11 boys and 11 girls were selected from classes 2-6, to achieve a desired sample of 110 children. In schools where the desired sample could not be achieved due to low enrolment, all the students in classes 2-6 were recruited.

3.3.1. Survey procedures

Selected children were asked to provide a finger-prick blood sample which was used to assess *Plasmodium* infection in peripheral blood in all the 480 schools while anaemia was assessed in a randomly selected sub-sample of 399 schools. Children had both a rapid diagnostic test (RDT) which gave an on-the-spot diagnosis for malaria and a thick and thin blood smear for subsequent microscopy. Different RDT types were used during the different survey phases. The majority (72.8%) of children were tested with either a ParaCheck-*Pf* device or a ParaCheck-*Pf* dipstick, while the rest were tested using OptiMAL-IT (17.3%) or CareStart Malaria P*f*/P*v* Combo (9.9%) RDTs. Blood slides were labelled and air-dried horizontally in a carrying case in the school, and stained with 3% Giemsa for 45 minutes at the nearest health facility at the end of each day. All the RDT positive microscopy slides and a random sample of RDT negative slides were examined by expert microscopists to ascertain *Plasmodium* infection. The RDT results were corrected using the microscopy results and the slide corrected RDT results were used as the definitive malaria diagnosis.

Using the same finger-prick sample haemoglobin concentration was assessed using a portable haemoglobinometer (Hemocue Ltd, Angelhölm, Sweden) and estimated to an accuracy of 1 g/L. A questionnaire was administered to children to obtain data on mosquito net ownership and use and whether the net was an ITN. Information was also collected on recent deworming, key socio-economic variables such as household construction and drinking water source. The children's responses were entered electronically into ASUS Eee PC 1005P or Acer Aspire One d250 netbook computers using a customized Microsoft Access database, and transmitted nightly to Nairobi through the mobile phone network. The geographical locations of schools were determined using a Garmin eTrex global positioning system (Garmin, Olathe, Kansas, USA).

Figure 3.1. The geographical distribution of the 480 sampled schools by malaria transmission zones in Kenya, as based on a geostatistical model of *Plasmodium falciparum* prevalence[14].



3.3.2. Ethical considerations

The study protocol received ethical approval from the Kenya Medical Research Institute and National Ethics Review Committee (#1407, 1596). Additional approval was provided by the appropriate national, provincial and district-level health and education authorities who were briefed about the survey. At the school level, parental consent was based on passive, opt-out consent rather than written opt-in consent owing the low risk and routine nature of the study procedures. Individual assent was obtained from each child before participation in the survey.

3.3.3. Data analysis

Analysis was done using Stata version 11.0 (Stata Corporation, College Station, TX, USA). *Plasmodium* infection and anaemia were assessed for their association with reported net use for each of the five malaria transmission zones. *Plasmodium* infection was defined on the basis of RDT results corrected with expert microscopy results. Anaemia was defined as haemoglobin concentration <130g/L for boys aged >15 years, <120 g/L for children aged 12-14 years and female children >15 years, <115 g/L for children aged 5-11 years and <110 g/L for children aged less than five years, with adjustment made for elevation of the children's school [15]. Mosquito net use was defined as any child who reported having slept under a net the night before the survey. For the purposes of the current analysis we assumed that all nets are treated nets. This is because the vast majority of nets used in Kenya today are treated nets [16-18]. Furthermore, in practical terms, children are unlikely to be able to distinguish whether nets are treated or not.

The country is stratified according to malaria transmission intensity based on a geostatistical model that combines available data on *P. falciparum* infection prevalence and ecological and climate covariates in a Bayesian model-based geostatistical framework to predict the prevalence of infection across Kenya for the year 2009 [14]. This model identifies five malaria transmission zones: lakeside high; coastal; western highlands epidemic; central low risk; and semi-arid. Estimates of school-level prevalence of hookworm infection were derived from a geostatistical model of hookworm prevalence [19], with prevalence stratified into low (0 – 21%) and high prevalence (>21) on the basis of the 90th percentile.

Prevalence estimates were estimated using random effects models to account for clustering occurring at the school level [20]. Prevalence estimates of *Plasmodium* infection and anaemia the proportion of children using nets were estimated using zero-inflated Poisson (ZIP) models to account for the excess of zero prevalence, while the proportion of children using nets was estimated using a multilevel mixed effects model. The ZIP model was favoured over the standard Poisson model on the basis of the Vuong test [13, 21]

Univariable analysis of risk factors for *Plasmodium* infection and anaemia was undertaken within each transmission zone separately for each outcome using mixed effects logistic regression. To select candidate covariates for multivariable analysis, an inclusion criterion of $p<0.1$ from a likelihood ratio test (LR test) was pre-specified after *a priori* inclusion of age, sex and net use. Covariates included mosquito net use, household wealth indicators such as household construction (floor and walls), availability of electricity and latrine access. In addition, data on altitude and location (whether urban or rural) of the school were entered into the malaria models while data on *Plasmodium* infection status, deworming history and school level estimated hookworm prevalence were also entered into the anaemia models. Backward-stepwise selection of covariates was used to generate minimum adequate models. Excluded covariates ($p>0.1$) were retested in the final models using LR tests to confirm lack of association; however, reported net use, age group and sex were retained as fixed terms in all models regardless of statistical significance because of their known importance.

After identifying covariates for inclusion in multivariate regression models within each transmission zone, three *a priori* interactions were investigated: 1) reported net use and sex and 2) reported net use and age group in both models; and 3) age and sex in the anaemia model. The existence of heterogeneity in the odds ratios according to sex, and age groups was assessed on the basis of likelihood ratio tests in multivariable models and interaction was included in the final model if $p<0.1$. Stratum specific odds ratios were derived from the final multivariable models.

3.4. Results

A total of 49,975 children from 480 schools were included in the surveys, but only 43,285 (86.6%) had complete data on all covariates of interest and therefore included in the analysis for *Plasmodium* infection. Data on anaemia were collected from 41,884 children in 399 schools and 98% of these had complete data and were therefore included in the anaemia analysis. A similar number of boys (50.7%) and girls were included (Table 3.1), and the median age was 11 years (inter quartile range: 10-13 years).

The overall microscopy-corrected RDT prevalence of *Plasmodium* infection was 4.4% (95% confidence interval [CI]: 3.4-5.4%), and the prevalence of anaemia was 24.0% (95% CI: 22.5-25.5%). The prevalence of infection was highest in lakeside zone and lowest in central and semi-arid zones, whereas anaemia was highest in the coastal and semi-arid zones (Table 3.1).Overall, 44.9% (95% CI: 42.9 - 47.0%) of children reported having slept under a net the night before the survey; 42.5% of boys and 46.1% of girls reported using a net. Net use varied by transmission zone being highest in the coastal zone and lowest in the lakeside zone (Table 3.1).

Table 3.1: The number of children examined, and the percentage of primary school children in Kenya infected with *Plasmodium spp.* infection and anaemic and reported using an insecticide treated net (ITN) by strata. 95% binomial confidence intervals (CIs)

	***Plasmodium* infection (n=43,285)**[1]			**Anaemia (n=40,885)**[2]		
	Number examined (%)	**Prevalence of *Plasmodium* infection[3] (95% CI)**	**Proportion net use[4] (95% CI)**	**Number examined (%)**	**Prevalence of anaemia[3] (95% CI)**	**Proportion net use[4] (95% CI)**
Plasmodium infection						
No	41,388 (95.6)	-	44.5 (42.4 – 46.6)	38,855 (95.0)	23.6 (22.1 – 25.1)	45.4 (43.2 – 47.7)
Yes	1,897 (4.4)	-	34.8 (31.4 – 35.4)	2,030 (5.0)	34.0 (30.7 – 37.4)	34.3 (31.1 – 37.6)
Anaemic						
No	-	-	-	31,025 (75.9)	-	45.6 (43.4 – 47.9)
Yes	-	-	-	9,860 (24.1)	-	44.5 (42.0 – 46.9)
Reported net use						
No	24,150 (50.7)	5.2 (4.0 – 6.4)	-	22,448 (54.9)	22.4 (20.8 – 24.0)	-
Yes	19,135 (49.3)	3.4 (2.6 – 4.2)	-	18,437 (45.1)	26.2 (24.4 - 27.9)	-
Sex						
Male	21,925 (50.7)	4.5 (3.5 – 5.5)	42.5 (40.3 – 44.6)	20,735 (50.7)	26.0 (24.3 - 27.6)	43.2 (41.0 – 45.5)
Female	21,360 (49.3)	4.3 (3.3 – 5.2)	46.1 (43.8 – 48.3)	20,150 (49.3)	22.2 (20.7 – 23.7)	47.1 (44.7 – 49.4)
Age group						
5 - 9 years	10,610 (24.1)	4.5 (3.4 - 5.7)	48.9 (46.5 – 51.3)	9,823 (24.0)	21.9 (20.1 - 23.8)	49.8 (47.4 – 52.3)
10 - 15 years	29,450 (68.0)	4.5 (3.5 - 5.5)	43.4 (41.2 – 45.6)	27,987 (68.5)	23.6 (22.1 - 25.1)	44.3 (42.1 – 46.6)
>15 years	3,225 (7.5)	3.1 (2.0 – 4.1)	39.3 (36.5 – 42.2)	3,075 (7.5)	36.0 (33.4 - 38.6)	40.3 (37.4 – 43.2)

Table 3.1 continued

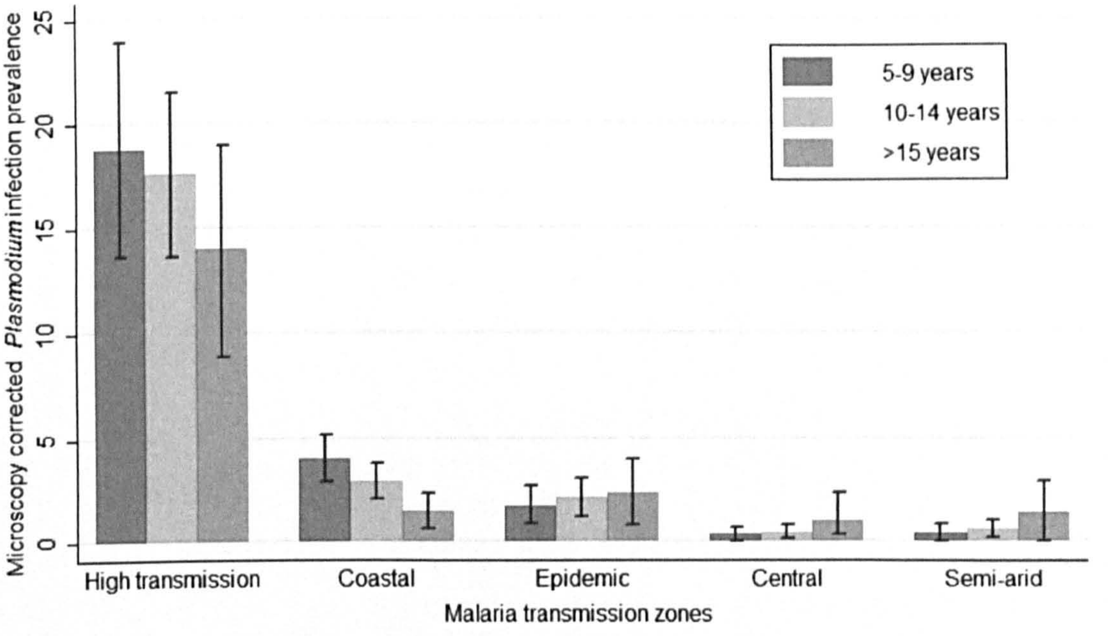
	Plasmodium infection (n=43,285)[1]			Anaemia (n=40,885)[2]		
	Number examined (%)	**Prevalence of *Plasmodium* infection[3] (95% CI)**	**Proportion net use[4] (95% CI)**	**Number examined (%)**	**Prevalence of anaemia[3] (95% CI)**	**Proportion net use[4] (95% CI)**
Malaria transmission zone[5]						
Lakeside high transmission	7,361 (17.0)	17.6 (13.5 - 21.6)	33.3 (30.1 – 36.6)	7,639 (18.7)	22.6 (19.6 – 25.5)	30.9 (27.9 – 33.9)
Coastal	9,797 (22.6)	2.8 (2.0 - 3.7)	63.0 (59.7 – 66.4)	9,626 (23.5)	39.2 (37.0 - 41.5)	63.0 (59.6 – 66.3)
Western highlands epidemic	10,578 (24.4)	2.3 (1.3 - 3.3)	35.5 (32.5 – 38.4)	8,480 (20.7)	11.4 (10.1 - 12.8)	37.8 (34.4 – 41.1)
Central low risk	10,879 (25.1)	0.5 (0.1 - 0.8)	38.7 (34.2 – 43.3)	10,477 (25.6)	13.4 (11.4 - 15.4)	40.1 (35.4 – 44.7)
Semi-arid north eastern	4,670 (10.8)	0.8 (0.3 - 1.4)	55.9 (48.8 – 63.0)	4,663 (11.4)	42.6 (39.0 - 46.2)	55.9 (48.8 – 62.9)

[1] 6,690 children excluded from the final analysis due to missing data
[2] 999 children excluded from final analysis due to missing data
[3] Prevalence and 95% confidence intervals estimated using a zero-inflated Poisson model adjusting for clustering at the school level.
[4] Proportion and 95% confidence intervals estimated using a multilevel random effects model adjusting for clustering at the school level.
[5] Zones based on a geostatistical model of *Plasmodium* prevalence in Kenya [14].

3.4.1. *Plasmodium* infection and its risk factors

The importance of different risk factors was found to vary by malaria transmission zone (Tables 3.2 and 3.3). In particular, *Plasmodium* infection differed significantly by age group only in the lakeside and coastal zones, with lower risk with increasing age (Figure 3.2 and Table 3.3). In the multivariable analysis, females had lower odds of infection in the lakeside zone and higher odds of infection in the coastal zone, but no association between sex and infection was found in other zones.

Figure 3.2. The prevalence of microscopy-corrected *Plasmodium spp.* infection in school children by age group across malaria transmission zones in Kenya, 2008 - 2010. Error bars indicate 95% binomial confidence intervals.



A significant association between *Plasmodium* infection and reported net use was observed in the coastal zone, with a 31% (95% CI: 10 – 47%) reduction in the odds of infection (p=0.006). Although there was evidence in the univariable analysis of a 15% reduction in the odds of infection in children who reported using nets in the lakeside zone (Table 3.2), this effect was not apparent after adjusting for potential confounders (Table 3.3). The results from the LR tests in the multivariable models indicated that there was borderline variation in the association between infection and net use by sex in the western highlands epidemic zone, with a 35% reduction in the odds of infection among male net users. In the central and semi-arid zones, there was no evidence of an association between net use and infection.

Lower odds of infection were associated with attending a school situated at an elevation of >1500 m in the western highlands epidemic zone whereas attending a school in an urban location was associated with higher odds of infection in the central zone. Finally, lower infection levels were associated with increased socio-economic status in all zones except in the semi-arid zone.

Table 3.2: Risk factors for Plasmodium infection among primary school children in Kenya stratified by malaria transmission zones, 2008-2010. Univariable odds ratios (OR) adjusted for clustering at the school level are shown with their corresponding 95% confidence intervals (95% CI).

	Lakeside high transmission (n=7,361)		Coastal (n=9,797)		Western highland epidemic (n=10,578)		Central low risk (n=10,879)		Semi-arid north eastern (n=4,670)	
	OR	P value	OR	P value	OR	P value	OR	P value	OR	P value
Reported net use										
No vs Yes	0.85 (0.73 – 0.99)	0.039	0.69 (0.54 – 0.90)	0.006	0.86 (0.62 – 1.18)	0.335	0.67 (0.32 – 1.34)	0.246	1.09 (0.55 – 2.16)	0.810
Sex										
Male vs Female	0.80 (0.69 – 0.92)	0.002	1.35 (1.05 – 1.74)	0.018	0.79 (0.59 – 1.05)	0.101	0.85 (0.47 – 1.53)	0.585	1.28 (0.66 – 2.49)	0.458
Age group										
5-9 years vs 10 - 15 years	0.80 (0.68 – 0.95)		0.58 (0.42 – 0.79)		0.82 (0.58 – 1.15)		1.35 (0.67 – 2.71)		1.66 (0.56 – 4.93)	
5-9 years vs >15 years	0.52 (0.36 – 0.75)	0.001	0.21 (0.12 – 0.38)	<0.001	0.63 (0.34 – 1.14)	0.268	1.68 (0.53 – 5.31)	0.601	2.50 (0.71 – 8.87)	0.354
Wall type										
Bricks/ cement vs Mud/clay/ other	1.57 (1.31 – 1.89)	<0.001	1.52 (1.03 – 2.25)	0.034	1.72 (1.00 – 2.96)	0.049	1.71 (0.68 – 4.30)	0.255	4.57 (0.60 – 34.98)	0.143
Floor										
Cement vs Earth/ wood/ iron sheets	1.61 (1.34 – 1.92)	<0.001	1.24 (0.84 – 1.82)	0.275	2.09 (1.20 – 3.65)	0.009	1.15 (0.48 – 2.73)	0.751	3.41 (0.44 – 26.45)	0.240
Drinking water source										
Piped vs Borehole/ well	1.13 (0.86 – 1.48)		1.48 (0.94 – 2.31)		2.04 (1.00 – 4.16)		0.94 (0.32 – 2.71)			
Piped vs Other[1]	1.15 (0.88 – 1.50)	0.589	1.56 (1.00 – 2.41)	0.131	1.89 (0.96 – 3.71)	0.140	1.24 (0.48 – 3.18)	0.824		

Table 3.2 continued

	Lakeside high transmission (n=7,361)		Coastal (n=9,797)		Western highland epidemic (n=10,578)		Central low risk (n=10,879)		Semi-arid north eastern (n=4,670)	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Electricity										
No vs Yes	0.47 (0.31 – 0.72)	0.001	0.51 (0.22 – 1.18)	0.116	1.15 (0.51 – 2.60)	0.738	2.70 (0.91 – 8.00)	0.075		
Latrine										
No vs Yes	0.90 (0.74 – 1.09)	0.293	0.56 (0.41 – 0.76)	<0.001	1.63 (0.70 – 3.78)	0.254	0.21 (0.09 – 0.51)	0.001	0.80 (0.38 – 1.75)	0.581
Urban										
No vs Yes	0.54 (0.17 – 1.72)	0.296	2.76 (0.63 – 12.14)	0.178	3.5 (0.39 – 30.60)	0.264	12.62 (1.44 – 110.48)	0.022	0.28 (0.01 – 8.46)	0.465
Altitude										
0 – 1500m vs >1500m	0.48 (0.18 – 1.23)	0.126	Omitted[2]		0.05 (0.01 – 0.23)	<0.001	1.34 (0.27 – 6.67)	0.718	Omitted[2]	

[1] Other water sources included from neighbours, community water tanks and buying
[2] Variables were omitted in the models because of collinearity

Table 3.3: Risk factors for Plasmodium infection among primary school children in Kenya stratified by malaria transmission zones, 2008-2010. Multivariable odds ratios (OR) adjusted for clustering at the school level are shown with their corresponding 95% confidence intervals (95% CI).

	Lakeside high transmission (n=7,361)		**Coastal (n=9,797)**		**Western highland epidemic (n=10,578)**		**Central low risk (n=10,879)**		**Semi-arid north eastern (n=4,670)**	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Reported net use										
No vs Yes	0.89 (0.76 – 1.05)	0.160	0.69 (0.53 – 0.90)	0.006	*		0.70 (0.34 – 1.45)	0.341	1.06 (0.53 – 2.13)	0.859
Sex										
Male vs Female	0.77 (0.67 – 0.89)	<0.001	1.39 (1.08 – 1.79)	0.011	0.64 (0.45 – 0.91)$	0.014	0.86 (0.47 – 1.56)	0.610	1.35 (0.69 – 2.65)	0.378
Reported net use by sex										
Males										
Net non-users vs Net users					0.65 (0.41-1.02)	0.062				
Females										
Net non-users vs Net users	-		-		1.14 (0.74 – 1.78)	0.537	-		-	
Age group										
5 - 9 years vs 10 - 15 years	0.79 (0.67 – 0.93)		0.54 (0.40 – 0.75)		0.80 (0.56 – 1.13)		1.30 (0.64 – 2.64)		1.75 (0.58 – 5.21)	
5 - 9 years vs >15 years	0.48 (0.34 – 0.70)	<0.001	0.18 (0.10 – 0.33)	<0.001	0.58 (0.32 – 1.06)	0.146	1.64 (0.51 – 5.29)	0.659	2.68 (0.75 – 9.57)	0.296
Floor										
Cement vs Earth/ wood/ iron sheets	1.52 (1.27 – 1.83)	<0.001	-		2.09 (2.00 – 3.65)	0.010	-		-	

Table 3.3 continued

	Lakeside high transmission (n=7,361)		Coastal (n=9,797)		Western highland epidemic (n=10,578)		Central low risk (n=10,879)		Semi-arid north eastern (n=4,670)	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Electricity										
No vs Yes	0.59 (0.39 – 0.91)	0.017	-		-		3.09 (0.88 – 10.85)	0.078	-	
Latrine										
No vs Yes	-		0.57 (0.42 – 0.78)	<0.001	-		0.15 (0.06 – 0.39)	<0.001	-	
Urban										
No vs Yes	-		-		-		6.29 (1.03 – 38.37)	0.046	-	
Altitude										
0 – 1500m vs >1500m	-		-		0.05 (0.01 – 0.22)	<0.001	-		-	
Likelihood ratio test for interaction between:										
Reported net use and sex		0.832		0.421		0.069		0.623		0.725
Reported net use and age group		0.887		0.145		0.250		1.000		0.167

-Variables excluded from the final model

* There was statistical evidence of an interaction; the stratum specific results are therefore reported.

$ Effect of sex on anaemia in non-net users

3.4.2. Anaemia and its risk factors

As expected, the risk factors for anaemia were found to vary according to malaria transmission zone (Table 3.4 and 3.5). In all zones, older children (>15 years) were associated with higher odds of anaemia while females had lower odds of infection in the western highlands epidemic and semi-arid zones (Table 3.5). In the coastal, western highlands and semi-arid zones there was evidence of an interaction between sex and age group (LR test $p<0.001$), indicating no differences in the odds of anaemia in younger children (5-9 and 9-15 years) by sex while among children aged >15 years, females had lower odds of infection.

Plasmodium infection was associated with higher odds of anaemia in the lakeside, western highlands epidemic and central zones. Reported net use was associated with lower odds of anaemia in coastal and central zones and among male net users in the lakeside zone; no association was evident in the western highlands epidemic and semi-arid zones (Table 3.5). Recent deworming was associated with lower odds of anaemia in coastal and central zones, with no evidence of an association in the other zones. There was statistical evidence of variation in the odds ratios for the association between reported ITN use and anaemia, by sex in the lakeside zone (LR test $p=0.051$), however there was no evidence of variation in the other zones or by age group.

Table 3.4: Risk factors for anaemia among primary school children in Kenya stratified by malaria transmission zones, 2008-2010. Univariable odds ratios (OR) adjusted for clustering at the school level are shown with their corresponding 95% confidence intervals (95% CI).

	Lakeside high transmission (n=7,639)		**Coastal (n=9,626)**		**Western highland epidemic (n= 8,480)**		**Central low risk (n=10,477)**		**Semi-arid north eastern (n=4,663)**	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Reported bed net use										
No vs Yes	0.89 (0.78 – 1.01)	0.067	0.91 (0.83 – 1.00)	0.044	0.87 (0.75 - 1.01)	0.077	0.83 (0.73 – 0.95)	0.008	0.95 (0.83 – 1.09)	0.483
Sex										
Male vs Female	0.94 (0.84 – 1.05)	0.248	0.72 (0.66 – 0.78)	<0.001	0.81 (0.71 – 0.93)	0.003	0.91 (0.80 – 1.02)	0.101	0.75 (0.66 – 0.84)	<0.001
Age group										
5 - 9 years vs 10 - 15 years	0.92 (0.81 – 1.05)		0.96 (0.85 – 1.08)		0.95 (0.80 – 1.12)		0.95 (0.83 – 1.08)		0.88 (0.75 – 1.02)	
5 - 9 years vs >15 years	1.30 (0.99 – 1.70)	0.020	1.27 (1.08 -1.49)	<0.001	1.88 (1.45 – 2.44)	<0.001	1.74 (1.34 – 2.27)	<0.001	1.48 (1.17 – 1.86)	<0.001
Plasmodium infection										
No vs Yes	1.54 (1.33 – 1.79)	<0.001	1.13 (0.87 – 1.46)	0.351	2.20 (1.57 – 3.09)	<0.001	3.02 (1.37 – 6.67)	0.006	1.05 (0.54 – 2.06)	0.876
Wall type										
Bricks/ cement vs Mud/clay/ other	1.07 (0.92 – 1.23)	0.379	1.09 (0.96 – 1.21)	0.232	1.04 (0.83 – 1.29)	0.754	0.99 (0.86 – 1.14)	0.899	1.20 (0.99 – 1.47)	0.064
Floor										
Cement vs Earth/ wood/ iron sheets	1.01 (0.88 – 1.16)	0.862	1.08 (0.95 – 1.21)	0.231	1.00 (0.82 – 1.22)	0.985	1.11 (0.96 – 1.29)	0.154	1.16 (0.95 – 1.41)	0.152

Table 3.4 continued

	Lakeside high transmission (n=7,639)		Coastal (n=9,626)		Western highland epidemic (n= 8,480)		Central low risk (n=10,477)		Semi-arid north eastern (n=4,663)	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Drinking water source										
Piped vs Borehole/ well	1.03 (0.81 – 1.30)		1.08 (0.94 – 1.23)		0.96 (0.70 – 1.32)		1.20 (0.96 – 1.49)		1.09 (0.83 – 1.42)	
Piped vs Other[1]	1.02 (0.82 – 1.28)	0.976	1.04 (0.92 – 1.19)	0.552	0.88 (0.67 – 1.17)	0.532	1.02 (0.84 – 1.25)	0.171	1.24 (0.96 – 1.61)	0.156
Electricity										
No vs Yes	0.76 (0.55 – 1.05)	0.098	0.99 (0.82 – 1.21)	0.953	0.95 (0.61 – 1.49)	0.831	0.80 (0.63 – 1.02)	0.071	0.93 (0.65 – 1.33)	0.703
Latrine										
No vs Yes	1.03 (0.88 – 1.19)	0.729	0.96 (0.88 – 1.07)	0.538	1.09 (0.82 – 1.44)	0.552	0.93 (0.77 – 1.11)	0.413	0.89 (0.77 – 1.02)	0.094
Dewormed in the last year										
No vs Yes	0.88 (0.72 – 1.07)	0.200	0.85 (0.77 – 0.93)	<0.001	1.02 (0.86 – 1.20)	0.832	0.81 (0.70 – 0.94)	0.005	0.91 (0.79 – 1.04)	0.150
Estimated hookworm prevalence										
0-21% vs >21%	1.30 (0.76 – 2.23)	0.338	1.09 (0.89 – 1.34)	0.384	0.80 (0.46 – 1.37)	0.414	Omitted[2]		Omitted[2]	

[1] Other water sources included from neighbours, community water tanks and buying
[2] Variables were omitted in the models because of collinearity

Table 3.5: Risk factors for anaemia among primary school children in Kenya stratified by malaria transmission zones, 2008-2010. Multivariable odds ratios (OR) adjusted for clustering at the school level are shown with their corresponding 95% confidence intervals (95% CI).

	Lakeside high transmission (n=7,639)		Coastal (n=9,626)		Western highland epidemic (n= 8,480)		Central low risk (n=10,477)		Semi-arid north eastern (n=4,663)	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Reported bed net use										
No vs Yes	*		0.91 (0.83 – 1.00)	0.048	0.90 (0.77 – 1.04)	0.150	0.86 (0.75 – 0.98)	0.023	1.01 (0.88 – 1.16)	0.912
Plasmodium infection										
No vs Yes	1.54 (1.33 – 1.79)	<0.001	-		2.24 (1.60 – 3.13)	<0.001	3.00 (1.35 – 6.66)	0.007	-	
Sex										
Male vs Female	0.89 (0.78 – 0.95)[1]	0.108	*		*		0.92 (0.82 – 1.03)	0.174	*	
Reported net use by sex										
Males										
Net non-users vs Net users	0.79 (0.66 – 0.95)	0.012	-		-		-		-	
Females										
Net non-users vs Net users	1.01 (0.85 – 1.20)	0.895	-		-		-		-	
Age group										
5 - 9 years vs 10 - 15 years	0.93 (0.81 – 1.06)		0.97 (0.82 – 1.14)[2]	0.677	1.05 (0.82 – 1.34)[2]	0.723	0.93 (0.81 – 1.06)	0.278	0.88 (0.71 – 1.10)[2]	0.266
5 - 9 years vs >15 years	1.34 (1.02 – 1.75)	0.017	3.38 (2.66 – 4.29)[3]	<0.001	2.53 (1.82 – 3.51)[3]	<0.001	1.67 (1.28 – 2.18)	<0.001	1.69 (1.25 – 2.28)[3]	0.001

Table 3.5 continued

	Lakeside high transmission (n=7,639)		Coastal (n=9,626)		Western highland epidemic (n= 8,480)		Central low risk (n=10,477)		Semi-arid north eastern (n=4,663)	
	OR	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**	**OR**	**P value**
Sex by age group										
5 - 9 years										
Male vs Female	-		0.92 (0.75 – 1.13)	0.428	1.05 (0.79 – 1.40)	0.735	-		0.83 (0.64 – 1.08)	0.157
10 - 15 years										
Male vs Female	-		0.88 (0.80 – 0.98)	0.015	0.87 (0.73 – 1.03)	0.109	-		0.77 (0.67 – 0.90)	0.001
>15 years										
Male vs Female	-		0.13 (0.10 – 0.17)	<0.001	0.36 (0.21 – 0.63)	<0.001	-		0.50 (0.34 – 0.74)	0.001
Wall type										
Bricks/ cement vs Mud/clay/ other	-		-		-		-		1.21 (0.99 – 1.47)	0.057
Dewormed in the last year										
No vs Yes	-		0.86 (0.78 – 0.94)	0.001	-		0.83 (0.72 – 0.97)	0.017	-	
Likelihood ratio test for interaction between:										
Net use and sex		0.051		0.270		0.113		0.669		0.274
Net use and age group		0.178		0.570		0.168		0.472		0.348
Sex and age group		0.181		<0.001		0.002		0.212		0.090

-Variables excluded from the final model on the basis, P value>0.1

* There was statistical evidence of an interaction; the stratum specific results are therefore reported.

[1]Effect of sex on anaemia in non-net users

[2]Effect of age in males, age group 5 -9 years vs 10 -15 years

[3]Effect of age in males, age group 5 -9 years vs >15 years

3.5. Discussion

To effectively target malaria control interventions, an understanding of the potential efficacy of interventions against malaria and related co-morbidities, such as anaemia, is necessary. To our knowledge, this study presents the first nationwide analysis of the association between reported net use, *Plasmodium* infection and anaemia in school children in a country with diverse malaria and nutritional ecologies. Results suggest that reported net use was associated with reduction in the odds of *Plasmodium* infection among all children in the coastal and there was borderline evidence of a 35% reduction in the odds of infection among males in the western highlands epidemic zone; no protective effect was observed in all other malaria transmission zones. Reported net use was associated with reduced odds of anaemia in the central and coastal zones, and among in males living in high lakeside zone.

Since completion of the current work, the results of the 2010 Kenya Malaria Indicator Survey (MIS) have been published [18]. Unlike in the 2007 MIS, this MIS assessed ITN use, malaria parasitaemia and anaemia among school-age children (5 -14 years). There are however notable differences in the findings of the 2010 MIS and our school survey results: for example, in the 2010 MIS, 34.2% and 27.8% of children reported sleeping under any net or ITN, respectively, whereas these figures were 44.9% and 19.0%. The disparity may be explained by temporal changes in bed net ownership and use, and the unreliability of school children reports on net treatment status. The 2010 MIS also reported a higher prevalence of infection: 13.3% based on microscopy compared to 4.4% in our school surveys. Such an increase may reflect temporal changes in transmission which is consistent with recent studies that have shown a rise in infection prevalence in the lakeside high transmission zone [22]. An in-depth analysis on the congruence between household surveys, such as those in the 2010 MIS, and school surveys in malaria surveillance is presented in detail in Chapter 6.

The observed lack of an association between net use and infection in the lakeside zone contrasts other studies that have reported a reduced risk of malaria infection among school-aged children who use nets [23, 24]. Possible factors for the lack of protective efficacy of nets in the lakeside zone include the high intrinsic intensity of transmission as well as low net use and poor quality of nets being used. For example, studies in Kenya indicate that school-age children are most likely to sleep under poor quality nets [25, 26] and household sleeping arrangements, such that school-aged children sleep on the floor and in areas where it is not possible hang nets, may affect the consistent use of nets by this age group [27, 28]. In addition, this study was done 2-3 years after the last mass distribution of LLINs in Kenya in 2006 and as has been shown in other studies [29, 30] the physical quality of nets in use deteriorates quickly. In high transmission zones, maintaining high ITN coverage and use in conjunction with complementary malaria interventions are required to effectively reduce malaria transmission and disease burden [31]. In 2008, indoor residual spraying was conducted in selected districts in the lakeside and western highlands zones in order to augment the effect of ITN distribution, while in 2011 mass distribution of LLINs aimed at universal coverage was conducted in the same districts. Within a school context, the use of intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) may additionally help reduce the burden of malaria in high transmission settings [32-37]. In central and semi-arid transmission zone, the cost-effectiveness of ensuring universal ITN coverage remains unclear due to low overall level of malaria transmission.

The effect of reported net use on anaemia is likely to be mediated by malaria transmission intensity and the presence of other aetiological factors for anaemia [38], including underlying nutritional factors [9], prevalence and intensity of helminth infection [11,39] and mix of helminth species [40]. Kenya is characterized by marked geographical diversity in such factors, including malaria [14], hookworm infection [19] and undernutrition [41]. In the lakeside and western highlands zones, where the prevalence of undernutrition is low and there are high prevalence of *Plasmodium* and helminth infections and coinfection [42], integrated malaria and helminth control programmes are likely to be beneficial [43]. In the coastal zone, integrated malaria and helminth control plus some form of school feeding and/or micronutrient supplementation is warranted [44]. Finally, in the central and semi-arid zones, it would seem that malaria and helminth control should be geographical targeted to only selected foci, but universal coverage of nutritional programmes would be beneficial.

The results also provide useful insight into the geographical variation in the relative importance of other risk factors for malaria and anaemia. Notably, there are differences in the magnitude and direction of the effect of risk factors such as sex, age, and socio-economic indicators. First, the observed differences in infection risk by age (Figure 3.2) are consistent with the exposure-related acquired immunity, with infection risk declining with age in high malaria transmission settings, and a similar risk among age groups in low transmission settings. Second, the sex differences in infection risk by zone lend weight to the importance of exposure-related factors in explaining sex differences in infection risk, rather than some intrinsic differences in susceptibility to infection [45]. Third, observed differences in the relative importance of the socio-economic indicator variables may reflect the difficulties of a composite socio-economic indicator index in a country with heterogeneous communities.

This study is not without its limitations. First, net use and net treatment status was not directly ascertained. This may lead to misclassification of net users and non-users and ITNs and non-ITNs therefore underestimating the effect size. However, a study in Uganda comparing school children's reports on bed net ownership and community based reports showed that school children can reliably report community-level bed net ownership [46]. Furthermore, the misclassification of ITNs and non-ITNs may be less of a problem as LLIN coverage increases with the assumption that most nets being used will be LLINs. The results from the 2010 MIS indicate that about 80% of nets in use are treated nets and therefore the misclassification of nets is unlikely to explain the observed results. Second, this study was conducted 2-3 years after the last mass distribution of nets in Kenya and the quality of bed nets was not assessed, therefore the observed protective effectiveness in our study could be an underestimation. Finally, the study utilizes data from a cross-sectional survey and is therefore subject to the caveats regarding inference and causality [47].

This chapter has demonstrated that the use of mosquito nets by school children varies markedly across Kenya and importantly, the estimated protective efficacy of nets against *Plasmodium* infection and anaemia differs according to malaria transmission zone. The findings emphasize the need for scaling up of ITN coverage in high and epidemic transmission zones, but that ITNs alone are unlikely to control malaria in such settings. In low transmission settings, by contrast, it is possible that the scaling up of ITN coverage alone may have a considerable impact on malaria transmission. There are however few studies on the impact of mosquito nets in low transmission settings, and there is also limited experience in the use of schools to distribute nets. The next chapter therefore explores the use schools as alternative distribution channels for mosquito nets and evaluates the impact of school-based distribution of nets on *Plasmodium* infection, anaemia and reported net use in an area of low malaria transmission in northeast Kenya.

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Chapter 4 : Impact of school-based delivery of long lasting insecticide nets on child health in an area of low, seasonal malaria transmission in coastal Kenya: a cluster randomized trial

4.1. Overview

As highlighted in Chapter 1, bed net delivery programmes in Africa have largely focused on children under the age of five years and pregnant women leading to inequitable net coverage, with school aged children being least likely to use bed nets. The subsequent chapters demonstrated that bed net coverage in Kenyan school children is low overall and there is marked geographical variation in use and in the potential efficacy of nets. There is a need therefore to increase net ownership and use to achieve tangible reduction in malaria burden, and to target programmes to areas of greatest need. To increase net ownership and use among school aged children, the existing school system can provide a complementary entry point for delivering nets to school children. However, there is little evidence on the impact of such strategy on net use and health of school children. This chapter reports results from a cluster randomised trial in Tana River and Tana Delta districts in coastal Kenya that evaluated the impact of distributing long lasting insecticide nets (LLIN) through schools on *Plasmodium* infection, anaemia and reported net use among school children.

This chapter has been submitted for publication in PLOS ONE: *Gitonga CW, Edwards T, Karanja PN, Allen E, Mwatele C, Okello G, Njagi JK, Kanjah A, Snow RWand Brooker SJ, 2012. Impact of school-based delivery of insecticide treated nets on child health in a* *low malaria transmission setting in Kenya: a cluster randomized trial. Submitted to PLOS ONE.* In this chapter, I was involved in the study design, planning, implementation and supervision of data collection and I undertook all data analysis.

4.2. Introduction

Research conducted in the last two decades has shown that insecticide treated nets (ITN) can significantly reduce early childhood mortality, as well as reducing rates of clinical malaria and anaemia in young children[1]. There is also evidence on health gains for pregnant women who use ITNs in Africa[2]. As a result of increased financial and political support, coverage of ITNs and more recently long lasting insecticide nets (LLINs) has increased dramatically in most malaria endemic countries[3]. To achieve this scale-up of coverage a variety of delivery systems have been employed, including subsidized nets through commercial retail sector, free mass distribution, free or highly subsidised nets through health facilities and through voucher systems[4-6]. However, achieving universal coverage, especially in poor and remote areas, has proved a particular challenge and there is a need to explore additional delivery mechanisms to expand coverage[7, 8].

The recent introduction of universal primary education in many sub-Saharan Africa countries has meant that even the poorest households are sending at least one child to school, providing a complementary, potentially equitable, mechanism through which to distribute LLINs, in support of exiting mechanisms. Targeting all community members, including school children, with LLINs may, in addition, yield enhanced health benefits[9]. Yet, there are few data on the potential efficacy of ITNs on malaria and anaemia in school age children despite this age group having the highest infection risk[10, 11] but least likely to sleep under a net[12, 13]. The few data that do exist show varying impacts of net use among school children. A 1988 randomised trial in an area of low malaria transmission in central Kenya showed that sleeping under untreated mosquito nets following a round of effective antimalarial treatment reduced the incidence of clinical malaria, but did not reduce anaemia, among children in a rural boarding school[14]. A reduction in the incidence of malaria was also shown in a randomised trial among 4-15 year olds on the Thai-Burmese border, where malaria transmission is unstable[15]. In western Kenya, where malaria transmission is perennial and high, a community-based trial of permethrin-treated mosquito nets in rural Western Kenya, showed that the use of ITNs halved the prevalence of mild all-cause anaemia in adolescent schoolgirls, aged 12 to 13 years[16], but was less effective in preventing anaemia among schoolgirls aged 6-10 years.

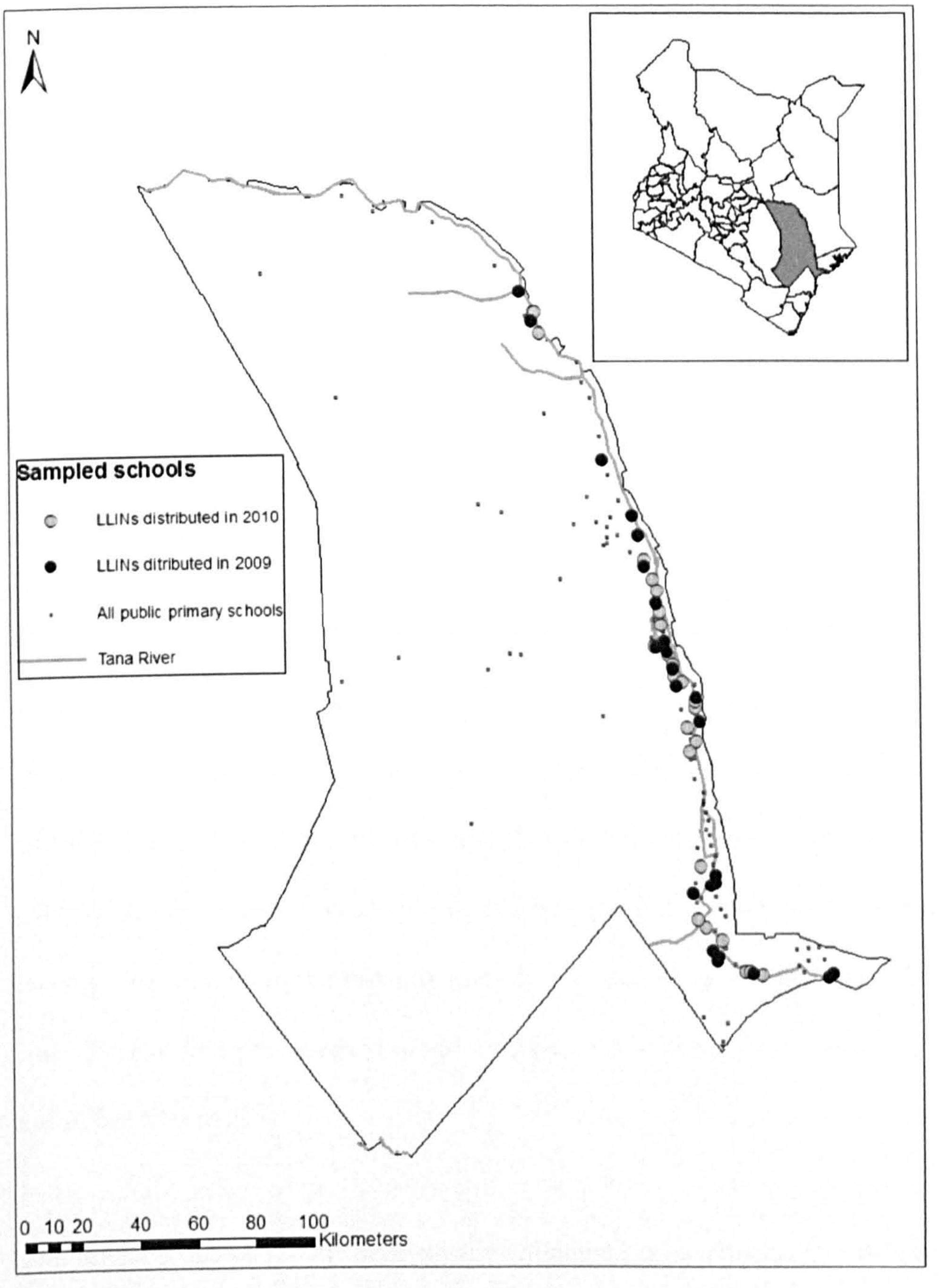
In Kenya, several ITN delivery strategies have been employed including the sale of subsidized nets through the commercial retail sector, highly subsidized and later free nets through the maternal and child health clinics and through free mass distribution of nets[5]. Although the ITN delivery strategies have been instrumental in increasing ITN coverage among the most vulnerable groups[4], there remains a huge gap in ITN coverage in Kenya[5]. The Government of Kenya was therefore interested in evaluating the potential of distributing nets through schools as a supplementary distribution system. In support of this interest, we conducted a school-based cluster randomized trial to evaluate the impact of distributing LLINs through schools on anaemia, *Plasmodium* infection and reported bed net use among primary school children in Tana River and Tana Delta districts in Kenya where malaria transmission intensity is low[17] and where LLIN coverage was previously low[18].

4.3. Materials and Methods

4.3.1. Participants

The study was conducted between February 2009 and March 2010 in 50 government primary schools in Tana River and Tana Delta districts in coastal Kenya (Figure 4.1). There are 130 government primary schools in the two districts and the majority (85.4%) of these schools are situated within 10 kilometres of the Tana River which originates from the footholds of Mt. Kenya and runs into the Indian Ocean. Malaria transmission is low and seasonal, with two seasonal peaks in malaria cases reflecting the bimodal rainfall pattern, with the heaviest rainfall typically occurring between April and June, with a smaller peak in October and November each year. Most malaria is caused by *Plasmodium falciparum*. There are few data on the malaria vectors in Tana River and Tana Delta districts, but the main vectors are likely to be *Anopheles arabiensis* and *Anopheles funestus* which are common in neighbouring areas[19]. The local population is mainly Pokomo who are typically subsistence farmers or Somali and Orma who are mainly pastoralists. Primary school officially starts at five years of age though some children do not enter schools until they are 7-8 years old. Children are taught for eight years, although some children repeat years and can remain in school up to the age of 18 years. Tuition is free but parents are required to pay fees for uniform and other fees such as school maintenance fees.

Figure 4.1: The geographical distribution of the 47 schools included in the analysis according to LLIN distribution phase. The schools are overlaid on the distribution of 130 public mixed day primary schools in Tana River district. Inset: A map of Kenya showing the location of Tana River district.



4.3.2. Sample size

The prevalence of anaemia was assumed to be 20% with a coefficient of variation of 0.25, based on results from a 2008 school survey in neighbouring Malindi District[20]. It was further assumed that 100 children per school could be assessed in a single day. Using the approach of Hayes & Bennett (1999)[21], this led to a sample size of 23 clusters per arm to provide 90% power to detect a 25% relative reduction in anaemia at 5% level of significance. This reduction was considered conservative since it is lower than the 50% reduction observed among adolescent girls involved in a community-based evaluation in western Kenya where malaria transmission is perennial and high[16].

4.3.3. Study design

A two-arm, cluster randomised trial was used to evaluate the impact of a programme delivering long lasting insecticide treated nets (LLINs) through schools on the prevalence of anaemia, prevalence of *Plasmodium* infection and school-level reported net use. Fifty government day mixed-sex primary schools were randomly selected from the 111 schools located within 10 km to the Tana River for inclusion in the study (Figure 4.1). Twenty five schools were randomly allocated to receive LLINs in August 2009 while the other 25 schools were assigned to serve as the control group and receive LLINs at the end of the trial in 2010.

Two repeat cross-sectional surveys were conducted, a baseline survey during February-March 2009 and a follow-up survey, 6 months after LLIN distribution, in February and March 2010. In each school, 110 children, 11 boys and 11 girls from classes 2-6, were randomly selected using computer-generated random number tables using Microsoft Excel. In schools where the number of enrolled students was less than the desired sample size, all the children in classes 2-6 were recruited. The selected children had a questionnaire administered and were asked to provide a finger-prick blood sample which was used to assess haemoglobin concentration and *Plasmodium* infection in the peripheral blood.

4.3.4. The intervention: LLIN distribution

LLINs were distributed in the 25 intervention schools between July and August 2009. Distribution of nets was conducted by Population Services International (PSI)-Kenya with support from the Ministry of Public Health and Sanitation (MoPHS) and the Ministry of Education (MoE). Prior to the distribution, PSI-Kenya contacted the district MoPHS and MoE officers, and the school heads to agree on the distribution dates and process. The LLINs were delivered to each school a week before the distribution and stored in the school stores. On the day of distribution, parents were invited to attend meetings during which district public health officers gave health talks on malaria and demonstrated how to hang nets before distributing them. School enrolment lists were used to estimate the number of children in the school and two nets, one for themselves and one for their younger siblings, were provided to each child.

4.3.5. Outcomes

Anaemia was the primary outcome and was defined as haemoglobin concentration <130g/L for boys aged >15 years, <120 g/L for children aged 12-14 years and female children >15 years, <115 g/L for children aged 5-11 years and <110 g/L for children aged less than five year [22]. Haemoglobin concentration was estimated to an accuracy of 1 g/L using a portable haemoglobinometer (Hemocue, Angelhölm, Sweden).

Plasmodium infection was a secondary outcome and was defined on the basis of malaria rapid diagnostic test (RDT) results corrected by expert microscopy. Children had both a malaria rapid diagnostic test which gave an on-the-spot diagnosis for infection with *Plasmodium* spp. and a thick and thin blood smears which were prepared for expert microscopy. Blood slides were labelled and air-dried in the school and stained with 3% Giemsa for 45 minutes at the nearest health facility at the end of each day. All blood slides of children with a positive RDT result and an equal random sample of slides from RDT negative children were examined by expert microscopy in Nairobi. Parasite densities were determined from thick blood smears by counting the number of asexual parasites per 200 white blood cells, assuming a white blood cell count of 8,000/μl. A smear was considered negative after reviewing 100 high-powered fields. Thin blood smears were examined for species identification. Two independent microscopists read the slides, with a third microscopist resolving discrepancies. The RDT result was corrected with the result from the expert microscopy and was used as the definitive diagnosis for *Plasmodium* infection.

Reported net use was a further secondary outcome and was defined as children who reported sleeping under a net the night before the survey. A questionnaire was administered to obtain data on mosquito net ownership and use, whether the net was an ITN, when it was obtained and where it was obtained from.

4.3.6. Other data collected

In the baseline survey, children were asked to provide stool samples which were examined in duplicate within one hour using the Kato-Katz technique for the eggs of intestinal nematodes, *Ascaris lumbricoides, Trichuris trichiura* and hookworm species, and the concentration of eggs were expressed as eggs/g (epg) of faeces. Height and weight were measured in the baseline survey using a portable stadiometer and an electronic balance, respectively.

Information was collected on key socio-economic variables such as household construction, household head occupation, ownership of livestock and mobile phones, availability of electricity, drinking water source and education level of the child's guardian. In May 2009, households of 70% of children that had been included in the baseline school survey were visited and net use was verified by visual inspection; however a follow-up household survey was not conducted as was in the protocol. The results of the household surveys will be reported separately. School survey data were entered electronically into ASUS Eee PC 1005P or Acer Aspire One d250 netbook computers using a customized Microsoft Access database, and transmitted nightly to Nairobi through the mobile phone network. Household survey data was collected using HP iPAQ 114 handheld personal digital assistants. The geographical location of each school was determined using a Garmin eTrex global positioning system (Garmin, Olathe, Kansas, USA).

4.3.7. Data analysis

Anthropometric indices were calculated using the WHO 2007 reference standards for 5-19 year olds, with stunting and thinness defined as z-scores <-2 SD for height-for-age and body mass index for age. Z-scores were computed using the WHO 2007 growth reference Stata macro[23]. A wealth index was constructed by assigning weights to reported household assets using principal components analysis (PCA). Variables on household construction (wall type, floor type and roof type), household assets (number of cows, goats, sheep, camels and donkeys, availability of a toilet, mobile phone and electricity), household head occupation and water source were included in the PCA and the first principal component was used to generate a PCA weight. Each child was then assigned to a specific wealth quintile, from the poorest to the least poor. The PCA was conducted separately for baseline and follow-up surveys.

Data were summarised to obtain school level prevalence estimates. By arm, data were then summarised as the mean and standard deviation (SD) of school-level summary estimates. Within-arm changes between baseline and follow-up were summarised as difference in means by arm with corresponding 95% confidence intervals (CIs) for anaemia, *Plasmodium* infection and reported net use.

Binomial generalised linear regression modelling on the odds scale, with robust standard errors was used to estimate the effect of the intervention on anaemia, *Plasmodium* infection and reported net use in unadjusted and adjusted analyses. Confirmatory analysis was done using mixed effects logistic regression models adjusting for clustering at the school level, Table 4.4. For anaemia, adjustments were made *a priori* for (school level) baseline measures of *Plasmodium* infection, anaemia, reported net use, infection with *A. lumbriciodes, T. trichiura* and hookworm, thinness and stunting and follow-up levels of mean age, proportion of boys and proportion of children who reported being de-wormed in the past year. In the *Plasmodium* infection model, baseline school-level measures of *Plasmodium* infection prevalence and net use as well as mean age and proportion of boys at follow-up level were adjusted for, while school-level mean age and proportion of boys at follow-up were adjusted for in the reported net use model.

All analysis was by intention to treat and was carried out using Stata version 11.0 (Stata Corporation, College Station, TX, USA).

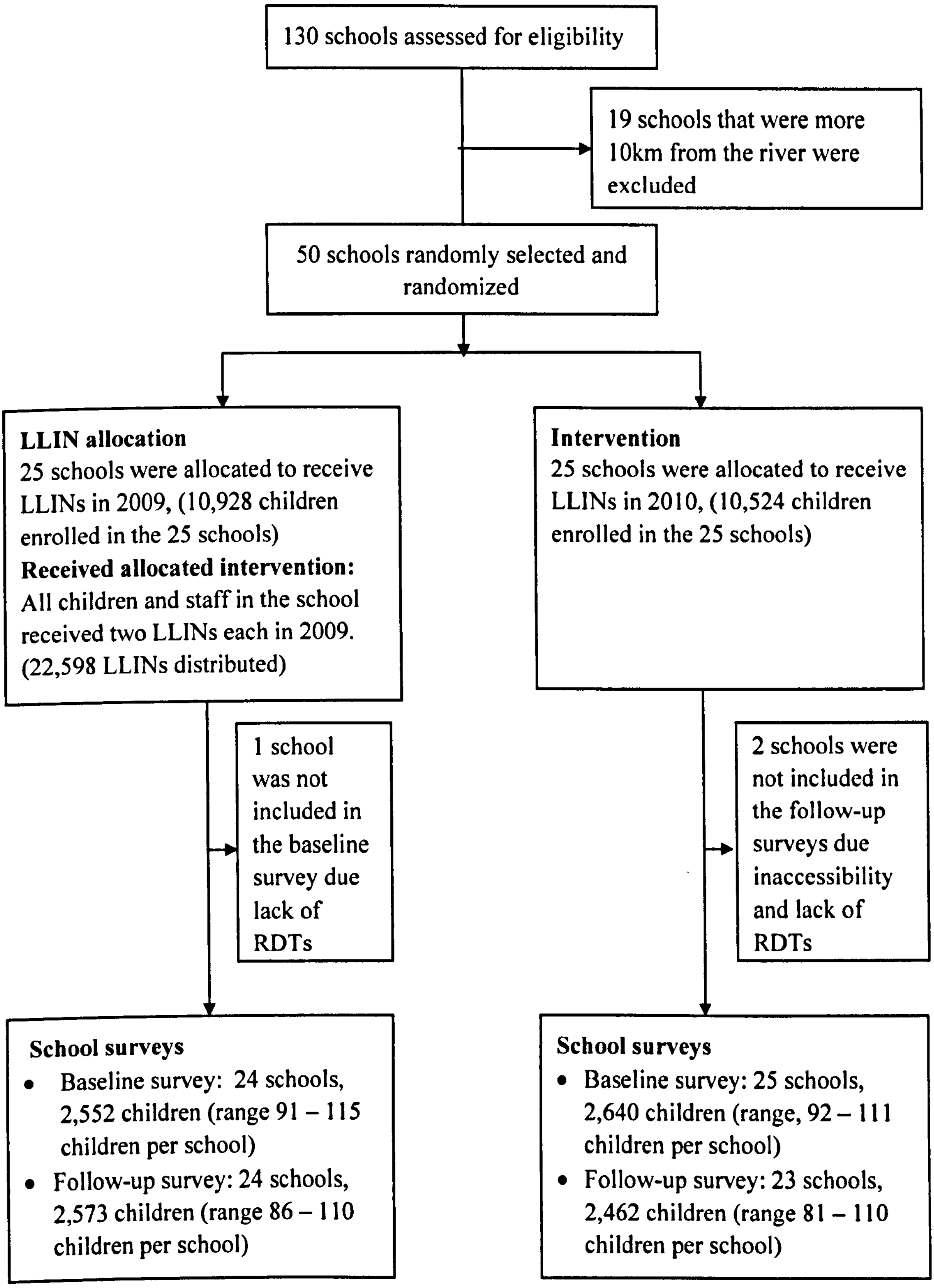
4.3.8. Ethical considerations

The study protocol received ethical approval from the Kenya Medical Research Institute and National Ethics Review Committee (SSC. 1596). Additional approval was provided by the Permanent Secretary's office of the Ministry of Education (MoE) and the Division of Malaria Control, Ministry of Public Health and Sanitation. After seeking permission from the head teachers, meetings were held in participating schools to explain the nature and purpose of the trial to parents or legal guardians and written consent was provided by the head of the parent-teacher association. Parents who did not wish their children to participate in the surveys were free to withdraw their children on the basis of opt-out consent. Individual assent was obtained from each child before assessments. During the household surveys, written consent was obtained by the household heads or a representative. The study was registered with ClinicalTrials.gov, number NCT00878397.

4.4. Results

The study profile is presented in Figure 4.2. Of the 50 schools selected for inclusion in the study, one school was not included in the baseline in February-March 2009 or follow-up survey February-March 2010 and an additional two schools were not included in the follow-up survey due to a lack of malaria rapid diagnostic tests (RDTs) and inaccessibility of the schools. From 49 schools a total of 5,113 children were included at baseline survey. At follow-up, 47 schools and 5,036 children were included in the survey and analysis. No systematic differences were observed in baseline covariates between the excluded and included schools (data not shown). An average of 105 children (range 90 – 115) was sampled per school in the baseline survey while an average of 106 children (range 64 – 110) was included in the follow-up survey (Table 4.1).

Figure 4.2: Study flow diagram



4.4.1. Baseline

Child characteristics summarised at school level were comparable between the intervention and control schools at baseline for socio-demographic and health measures and for outcome measures (Table 4.1). The mean school-level prevalence of anaemia was 21.3% (95% CI: 18.5 – 24.1%) in the control schools and 24.3% (95% CI: 20.2 – 28.4) in the intervention schools at baseline. The mean school-level prevalence of *Plasmodium* infection was low, with negligible observed differences between intervention schools and control schools, Table 4.1. The mean school-level bed net ownership was 64.2% (95% CI: 56.2 – 72.3%) in the control schools and 70.6% (95% CI: 61.5 – 79.6%) in the intervention schools.

Table 4.1: School level characteristics of children included in the baseline survey based on 49 schools.

	Control	Intervention
Number of schools	25	24
Number of children examined	2,640	2,552
Age, mean(SD)	11.2 (0.5)	11.5 (0.7)
Males , mean (SD)	50.0 (4.9)	51.7 (6.1)
Hb concentration (g/L), mean (SD)	118.6 (2.7)	118.3 (3.9)
Anaemia, mean (SD)	21.3 (6.7)	24.3 (9.8)
Plasmodium infection , mean (SD)	0.8 (2.0)	0.8 (2.0)
Reported net ownership, mean (SD)	67.3 (19.9)	75.4 (20.4)
Reported net use , mean (SD)	64.2 (19.5)	70.6 (21.4)
Dewormed in the last year	41.4 (19.9)	43.7 (19.9)
Stunting , mean (SD)	19.2 (10.7)	19.1 (9.2)
Thinness, mean (SD)	22.9 (15.5)	31.6 (18.1)
Hookworm prevalence, mean (SD)[1]	5.4 (8.7)	5.2 (9.4)
A. lumbriciodes prevalence, mean (SD)[1]	3.1 (9.7)	3.1 (12.5)
T. trichura prevalence, mean (SD)[1]	13.8 (19.0)	16.9 (21.2)
Anyworm prevalence, mean (SD)[1]	17.3 (20.8)	19.9 (22.8)
Socio-economic status, mean (SD)		
Poorest	21.5 (12.6)	18.1 (11.0)
Poor	19.4 (11.8)	20.6 (10.0)
Median	20.1 (7.0)	20.6 (9.7)
Less poor	20.2 (10.4)	19.9 (8.7)
Least poor	18.9 (18.4)	20.8 (17.9)

Mean (SD): Mean and standard deviation of the school level prevalence or mean
[1]Mean and SD based on 23 schools in the intervention arm

4.4.2. Follow-up

Child characteristics summarised at school level were also comparable between the intervention and control schools at follow-up. There were similar increases in the prevalence of anaemia in the follow-up survey from baseline in both control and intervention schools (control arm: mean increase of 31.5% (95% CI: 25.7 - 37.3) schools and intervention arm: mean increase of 29.5% (95% CI: 25.0 - 34.2), Table 4.2 and Figure 4.3a). The school-level mean prevalence of *Plasmodium* infection was low in both arms (1.1% (95% CI: 0.2 – 2.0) in the control schools vs 0.9% (95% CI: 0.1 – 1.7) in the intervention schools), with no differences between the intervention and control schools at follow-up. The majority (78.7%) of schools had no children with detectable *Plasmodium* infection (Figure 4.3b).

Table 4.2: School-level characteristics of children included in the follow-up survey based on 47 schools.

	Control	**Intervention**
Number of schools	23	24
Number of children examined	2,462	2,573
Age, mean(SD)	11.4 (0.5)	11.4 (0.6)
Males , mean (SD)	50.9 (2.4)	52.1 (5.1)
Hb concentration (g/L), mean (SD)	116.5 (3.0)	115.7 (3.3)
Anaemia, mean (SD)	52.9 (12.4)	53.8 (9.3)
Plasmodium infection , mean (SD)	1.1 (2.2)	0.9 (1.8)
Reported net ownership, mean (SD)	81.4 (15.6)	87.3 (12.0)
Reported net use , mean (SD)	72.6 (18.0)	85.1 (12.9)
Plasmodium infection , mean (SD)	1.1 (2.2)	0.9 (1.8)
Dewormed in the last year	56.1 (17.7)	50.9 (18.5)
Socio-economic status, mean (SD)		
Poorest	22.5 (15.0)	20.1 (12.5)
Poor	18.5 (11.0)	22.8 (11.0)
Median	20.3 (7.4)	22.9 (7.3)
Less poor	22.5 (11.8)	22.2 (10.6)
Least poor	23.3 (24.1)	19.2 (19.6)

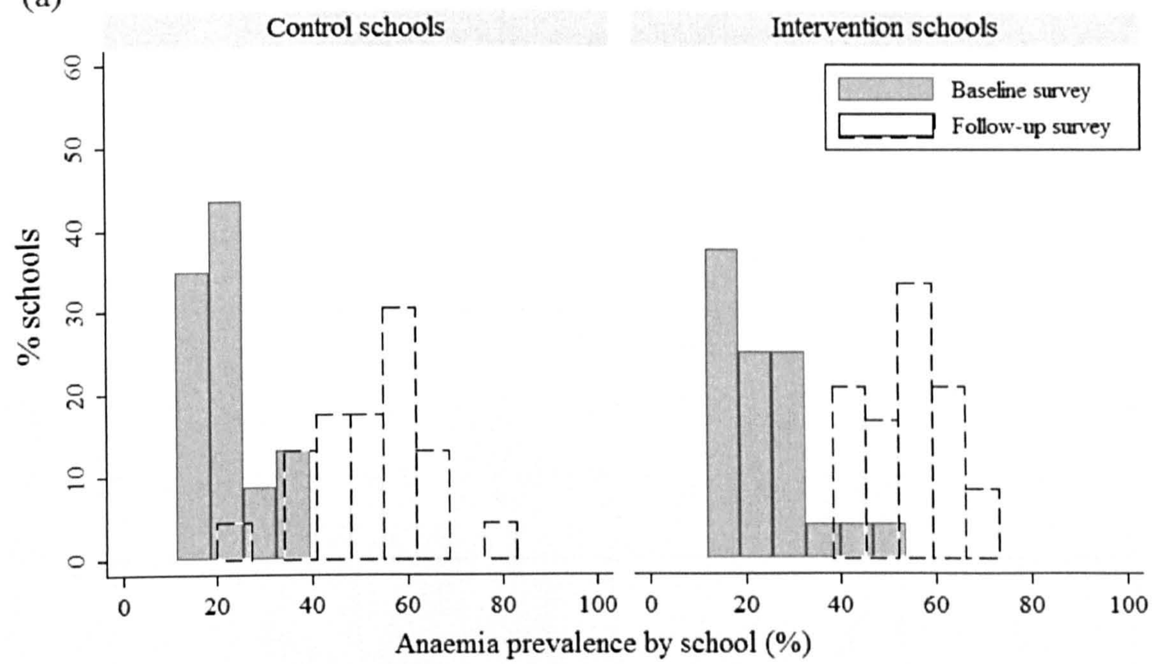
Mean (SD): Mean and standard deviation of the school level prevalence or mean

There was an increase in reported bed net ownership in both arms of the study at follow-up (mean increase in net ownership, analysed at school-level was 11.9% (95% CI: 3.4 –

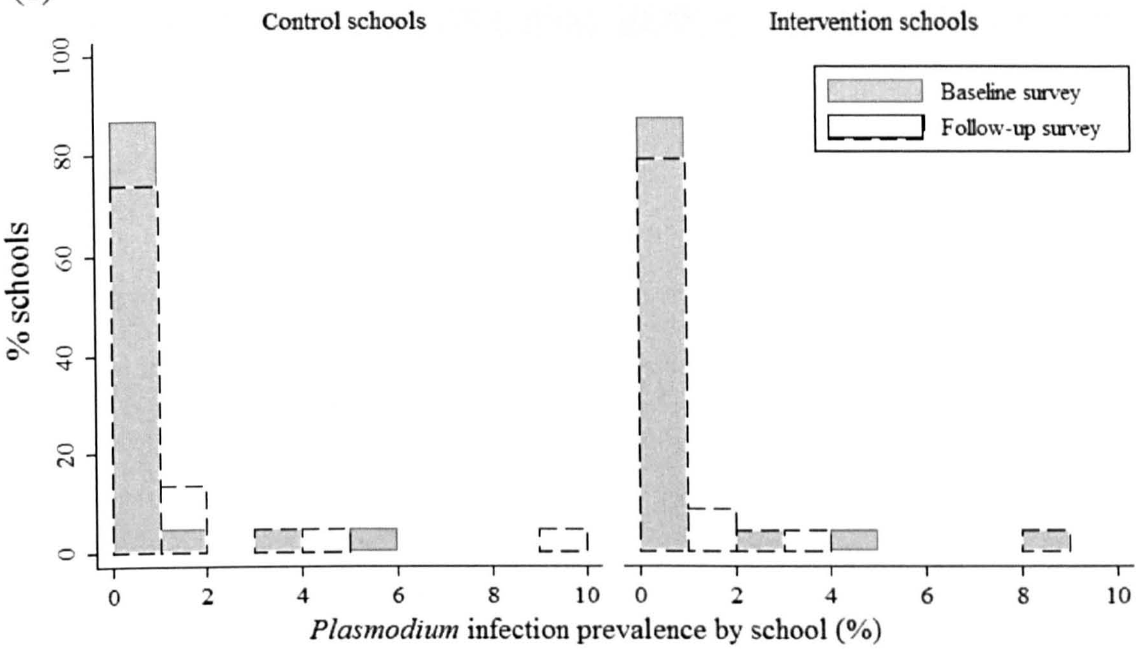
20.3%) in the intervention schools and 7.9% (95% CI: 1.2 – 14.6% in control schools). Similarly, there was an increase in children who reported using a net the night before the survey in both study arms (mean increase in reported bed net use of 14.6% (95% CI: 5.5 – 23.6%) in the intervention schools and 8.0% (95% CI: 1.8 – 14.3%) in control schools), Table 4.2 and Figure 4.3c.

Figure 4.3: Distribution of the school-level prevalence of (a) anaemia, (b) *Plasmodium* infection based on microscopy-corrected RDT results and (c) reported net use among school children in coastal Kenya at baseline (2009) and follow-up (2010).

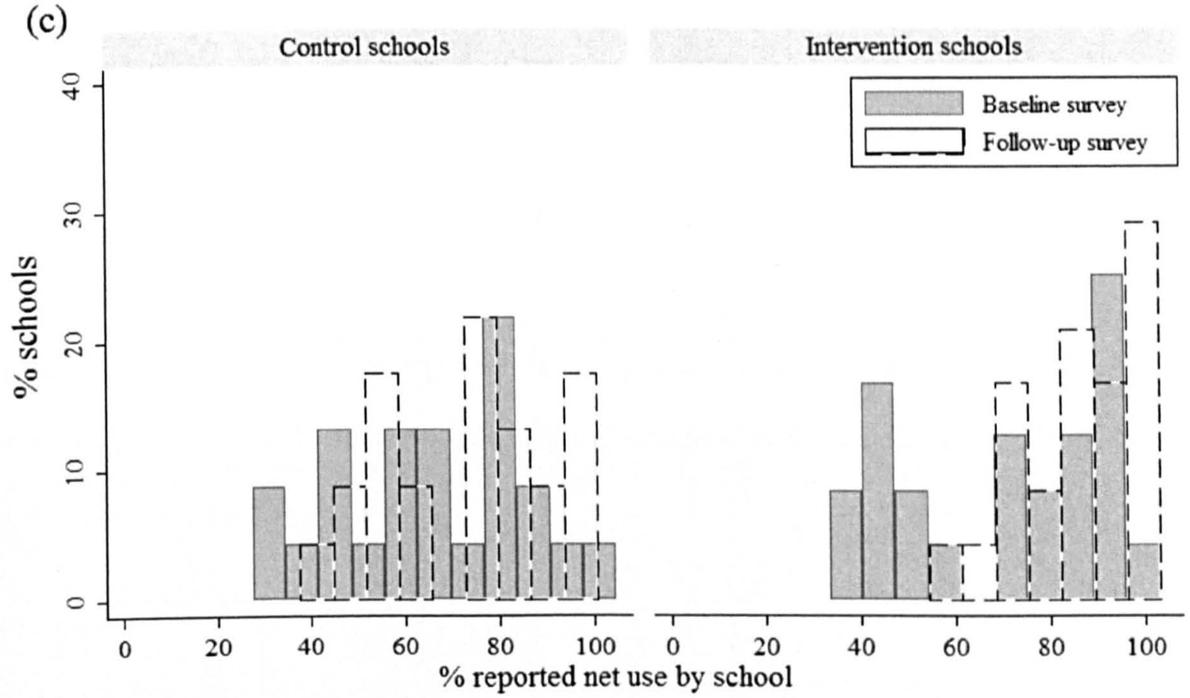
(a)



(b)



(c)



Unsurprisingly, 66.8% of nets in use in the intervention group were reported to have been obtained from school, while only 7.0% of nets in use in the control schools were reported to have been obtained from school. The other nets in use were reported to have been obtained from various sources including health facilities (19.7% in the intervention schools vs 62.2% in the control schools), shops (6.4% in intervention schools vs 19.4 in the control schools) and NGOs/community programmes (7.1% in the intervention schools vs 10.9% in the control schools). Almost half (45%) of the nets that were in use in the control schools were reported to have obtained more than a year before the survey, compared to only 21% in the intervention schools.

There were also increases in the proportion of children who reported having been dewormed in the last year at follow-up, (control arm: mean increase of 13.6% (95% CI: 1.5 – 28.8%) intervention arm: mean increase of 7.1% (95% CI: -4.2% - 18.5%).

4.4.3. Impact of LLIN distribution through schools

LLIN distribution through schools did not appear to have an impact on the prevalence of anaemia (adjusted odds ratio=0.87, 95% CI: 0.73 – 1.03) or the prevalence of *Plasmodium* infection (adjusted odds ratio=0.55, 95% CI: 0.23 – 1.35) in intervention schools compared to control schools, in either the unadjusted or adjusted analyses (Table 4.3). However, children in the intervention schools were more than twice as likely to report sleeping under a net the night before the survey, than children in the control schools 6 months post LLIN distribution through schools (adjusted odds ratio=2.26, 95% CI: 1.31– 3.92, Table 4.3).

Table 4.3: The effect of LLIN distribution through schools on anaemia, *Plasmodium* infection and reported net use, in Tana River and Tana Delta districts in Kenya: 2009-2010.

	Baseline		Follow-up		Intervention effect: Intervention vs control[2]			
	Control	Intervention	Control	Intervention	Unadjusted odds ratio (95% CI)	P value[6]	Adjusted odds ratio (95% CI)	P value[6]
Number of schools	25	24	23	24				
Number of children examined	2,640	2,552	2,462	2,573				
Anaemia, mean (SD)[1]	21.3 (6.7)	24.3 (9.8)	52.9 (12.4)	53.8 (9.3)	1.05 (0.82 – 1.35)	0.705	0.87 (0.73 – 1.03)[3]	0.103
Plasmodium infection, mean (SD)[1]	0.8 (2.0)	0.8 (0.8)	1.1 (2.2)	0.9 (1.8)	0.81 (0.25 – 2.61)	0.729	0.55 (0.23 – 1.35)[4]	0.192
Reported net use, mean (SD)[1]	64.2 (19.5)	70.6 (21.4)	72.6 (18.0)	85.1 (12.9)	2.23 (1.29 – 3.85)	0.004	2.26 (1.31 – 3.92)[5]	0.003

[1] Mean and standard deviation of the school level means
[2] Odds ratios based on binomial generalised linear regression with robust standard errors adjusted for clustering at the school-level.
[3] Adjusted for school level mean age at follow-up, proportion of boys at follow-up, proportion of children who reported having been de-wormed the year preceding the follow-up survey, and baseline covariates including school level *Plasmodium* infection, anaemia, reported net use, *A. lumbriciodes, T. trichiura,* and thinness.
[4] Adjusted for *Plasmodium* infection and net use at baseline, and mean age, proportion of boys at follow-up.
[5] Adjusted for mean age and proportion of boys at follow-up
[6] Wald test P value

Table 4.4: Confirmatory analysis of the effect of LLINs distributed through schools on anaemia, *Plasmodium* infection and reported net use, in Tana River and Tana Delta districts in Kenya: 2009-2010. The results from a binomial generalised linear regression model with robust standard errors adjusted for clustering at the school-level and a random effects model adjusted for clustering at the school level are reported.

	Intervention effect: binomial regression model				**Intervention effect: random effects model**			
	Unadjusted odds ratio (95% CI)	**P value**	**Adjusted odds ratio (95% CI)**	**P value**	**Unadjusted odds ratio (95% CI)**	**P value**	**Adjusted odds ratio (95% CI)**	**P value**
Anaemia[1]	1.05 (0.82 – 1.35)	0.705	0.87 (0.73 – 1.03)	0.103	1.04 (0.81 – 1.35)	0.742	0.87 (0.73 – 1.02)	0.092
Plasmodium infection[2]	0.81 (0.25 – 2.61)	0.729	0.55 (0.23 – 1.35)	0.192	0.88 (0.24 – 3.29)	0.853	0.67 (0.28 – 1.62)	0.382
Reported net use[3]	2.23 (1.29 – 3.85)	0.004	2.26 (1.31 – 3.92)	0.003	2.65 (1.33 – 5.28)	0.006	2.67 (1.34 – 5.34)	0.005

[1] Adjusted for school level mean age at follow-up, proportion of boys at follow-up, mean number of children who reported having been de-wormed the year preceding the follow-up survey, and baseline covariates including school level means of *Plasmodium* infection, anaemia, reported net use, *A. lumbriciodes, T. trichiura,* and thinness.

[2] Adjusted for *Plasmodium* infection and net use at baseline, and mean age, proportion of boys at follow-up.

[3] Adjusted for mean age and proportion of boys at follow-up

4.5. Discussion

ITN delivery strategies in Africa have justifiably been targeted to the most vulnerable groups, children under the age of five years and pregnant women, but this has resulted in an inequitable coverage of interventions, with school-age children being the least protected by ITNs[12]. In this cluster randomised study, we found that school-based distribution of nets resulted in an increase in reported net use and to use of new nets, but in the transmission setting where the trial was conducted, this did not result in a reduction in the odds of anaemia or *Plasmodium* infection in intervention schools compared to control schools.

There are a number of possible explanations as to why the increase in net use did not result in health improvements. First, there were exogenous changes in the nutritional status of the study population. According to reports from the famine early warning systems (FEWS) in Kenya[24], households in the study districts moved from being 'highly food insecure' in January-July 2009, to being 'extremely food insecure' in August to December 2009. This was caused by a combination of factors including failed rains, high food prices, crop failure, conflict and decreased livestock prices. Although these districts have school meals programmes, the meals consist of a diet of maize and beans which at times is shared with other family members. This change in food insecurity was the likely contributing factor to the observed increase in the levels of anaemia in both intervention and control schools. The lack of rain is also a likely factor in the marked reduction in the prevalence of *Plasmodium* infection observed in both groups.

Several design limitations should be considered in the interpretation of the current results. First, randomisation and analysis of the effect of LLIN distribution was done at the school level and this has greater potential for bias than studies in which randomisation is done at the individual level, such as earlier trials in western Kenya[14, 16] and the Thai-Burmese border[15]. Second, no attempt was made to ensure use of the study LLINs in children in the intervention schools and therefore the effect of LLINs on anaemia and *Plasmodium* infection may have been underestimated due to non-compliance; our results indicate that only 66% of nets in use by children from the intervention schools were been obtained from school. Thirdly, the sample size calculation was based on the main outcome, anaemia, and therefore the study lacked sufficient power to detect any changes in *plasmodium* infection prevalence due to the low prevalence.

Notwithstanding the role of external factors influencing levels of anaemia and *Plasmodium* infection, the findings from this study provide useful insight on the use of the existing school system as complementary approach for LLIN distribution. Notable is that children in the intervention schools were more than twice as likely to report using a net the night before the survey and were more likely to use newer nets indicating that the nets obtained from school were likely to replace old nets, suggesting that school children were the potential beneficiaries of the nets distributed through schools (assuming that the nets reported to have been obtained from school within a year of the follow-up survey, were the study nets). The existing ITN/LLIN delivery strategies in Africa - which include commercial markets, social marketing, mass distribution of free LLINs, free or highly subsidised nets through health facilities and voucher systems - have been suboptimal in achieving universal coverage and generally have not reached the school age population [12]. An increasing number of surveys show that the school-age population in Africa is least covered with LLINs [12, 25-28] and the few children who use nets are more likely to use damaged nets [26, 27]. The use of the existing school system therefore presents a potentially practical and equitable approach to scale up ITN coverage in the school age population.

The results suggest that the level of malaria transmission in the two districts and the potential health benefits may not be sufficient to warrant mass distribution of LLINs/ITNs. These results are consistent with our recent analysis of net use across different settings in Kenya that indicated that increasing net use among school children is likely to have the largest impact in areas of high malaria transmission [29]. In low transmission areas the costs of mass distribution of LLINs may outweigh the potential health benefits especially in resource limited settings [5]; targeting LLIN distribution in the small pockets of transmission in such areas may be more beneficial. However there is a need to further evaluate the cost-effectiveness of ensuring universal LLIN coverage in low transmission settings.

Although our study was affected by the prevailing drought in the study districts and there was no observed impact of LLINs distribution on health outcomes, our study provides supporting evidence that the existing school system can be used as a complementary system to increase access to LLINs in the school-age population. Further studies of school-based distribution in different transmission settings are warranted. The targeting of such distributions, as well as other school-based malaria interventions, should be based on reliable and up-to-date epidemiological information to ensure interventions are targeted according to intensity of malaria transmission. Building on Chapter 2, the next two chapters evaluate the reliability of school surveys to provide such data, with a particular focus on the reliability of rapid diagnostic tests for diagnosing infection (Chapter 5) and school children's reports of bed net use (Chapter 6).

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Chapter 5 : The use of rapid diagnostic tests in malaria school surveys in Kenya: does their under-performance matter for planning malaria control?

5.1. Overview

For school surveys to provide a reliable and inexpensive tool for malaria surveillance there needs to be a simple, quick, cheap and accurate method of diagnosing malaria infection. Rapid diagnostic tests (RDTs) offer an inexpensive, rapid and simple diagnostic tool but, as outlined in Chapter 1, are not without their limitations and can yield false positives leading to overestimation of infection prevalence. Using data from Chapter 2, this chapter evaluates the reliability of RDTs for estimating the prevalence of *Plasmodium* infection and explores the cost implications of alternative diagnostic strategies, including RDTs, microscopy-corrected RDT results, expert microscopy and polymerase chain reaction (PCR), for use in school-based malaria surveillance.

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5.2. Introduction

Rapid diagnostic tests (RDTs) based on malaria parasite antigen detection are now a key tool in the case management of clinical malaria[1], especially at lower level peripheral health facilities where routine microscopy is absent or of poor quality[2-5]. RDTs are also shown to be more cost-effective in improving health outcomes than expert microscopy in most sub-Saharan African settings[6]. In addition to their clinical use, RDTs are increasingly being used in epidemiological surveys of *Plasmodium* parasite infection as part of national monitoring and evaluation efforts. For example, of the 27 recent national malaria indicator surveys conducted in sub-Saharan Africa since 2006, RDTs were used in 19 surveys and in three of these surveys *Plasmodium* infection prevalence was estimated on the basis of RDTs alone[7-9]. The use of RDTs in large-scale surveys is preferable for therapeutic reasons as they provide point-of-contact diagnosis and, if required, immediate treatment. Moreover, RDTs overcome the human and technical capacity constraints faced by large-scale surveys in the use of expert microscopy in terms of quality staining and reading of thousands of blood slides and the logistics and costs associated with slide transportation, preparation, duplicate reading and quality assurance[10].

A well-recognized limitation of RDTs, especially those tests that detect the parasite antigen histidine-rich protein 2 (HRP-2) specific to *Plasmodium falciparum*, is the occurrence of false positive results due to persistent antigenaemia even after effective anti-malarial treatment[10]. Whilst such false positives of RDTs may have limited relevance for clinical case management, they will overestimate the true parasite prevalence compared to expert microscopy or molecular parasite detection techniques[10]. This is principally because RDTs that detect HRP-2 antigen cannot distinguish between active infections and resolved infections due to persistent antigenaemia therefore the observed prevalence may be indicative of prevalence over a period of time rather than point prevalence. Previous evaluations of RDTs in population-based household surveys among healthy individuals in Ethiopia[11] and Zambia[12] reported false positive rates of 1.5% and 7.9%, respectively against microscopy. Such findings raise an important operational question: does the false-positivity associated with RDTs matter when it comes to stratifying areas according to malaria risk in the geographical targeting of malaria intervention strategies? The answer to this question determines whether malaria control can be guided by community or school-based surveys using RDTs alone[13, 14].

In order to resolve the question of the usefulness of using RDTs in school malaria surveys there is a need for understanding two issues: (i) what is the occurrence of areas being misclassified in terms of intervention strategy when based on surveys using only RDTs compared to surveys using expert microscopy; and (ii) what are the cost implications of different diagnostic approaches used in school malaria surveys to guide malaria control? To help address these issues, here I examine the performance of three different RDTs used during a nationwide school malaria survey in Kenya[14] and investigate the cost implications of alternative diagnostic strategies, including RDTs, microscopy-corrected RDT results, expert microscopy and polymerase chain reaction (PCR), for use in future monitoring and evaluation approaches that focus on sentinel schools.

5.3. Methods

Malaria surveys were undertaken in 480 schools across Kenya between September 2008 and March 2010, described in detail elsewhere[14]. In brief, 11 boys and 11 girls were randomly selected in classes 2 - 6 to achieve a target sample of 110 children from each school. Ethical approval for the school surveys was obtained from the Kenya Medical Research Institute and Scientific and Ethics Review Committees. Consent for participation was based on passive, opt-out consent by parents rather than written, opt-in consent because of the routine, low-risk nature of the surveys that were conducted under the mandate of the Ministry of Public Health and Sanitation to conduct disease surveillance. Individual assent from the students was obtained before sample collection.

5.3.1. Survey procedures

In all schools, students were asked to provide a finger prick blood sample which was used to assess *Plasmodium* infection in the peripheral blood using RDTs. Four types of RDTs were used in the surveys depending on availability: (i) OptiMal-IT (Diamed, AG, Switzerland), which uses monoclonal antibodies against the metabolic enzyme parasite lactate dehydrogenase (pLDH) of *Plasmodium* spp., one specific for *P. falciparum* and the other, pan-specific monoclonal antibodies that react with *P. falciparum, P. vivax, P. ovale, P. malariae*; (ii) Paracheck-Pf device (Orchid Biomedical Systems, Goa, India), which detects the *P. falciparum* antigen histidine rich protein 2 (HRP-2); (iii) Paracheck-Pf dipstick, which detects the *P. falciparum* antigen histidine rich protein 2 (HRP-2); and (iv) CareStart *Pf/Pv* combo Access Bio, USA which uses monoclonal antibodies specific to *P. vivax* pLDH and P. *falciparum* HRP-2. Table 5.1 shows the number of children examined using each of the different RDT types by prevalence category. However, CareStart RDTs were found to have very poor specificity (38.1%) against microscopy, with the results presumed to reflect a spoiled batch and were therefore excluded from further analysis. Children with positive RDT results and documented fever were immediately treated with artemether-lumefantrine (Coartem, Novartis, artemether 20 mg/ lumefantrine 120 mg) according to national guidelines. Thick and thin blood films for microscopy were also prepared from the same finger prick blood sample.

Table 5.1: The number of children examined using different RDT types by *Plasmodium* infection prevalence category based on microscopy-corrected RDT results during school malaria surveys in Kenya, 2008 - 2010. The corresponding percentages are shown in parenthesis.

***Plasmodium* prevalence category**	**Paracheck *Pf* device**	**Paracheck *Pf* dipstick**	**OptiMal-IT *Pf*/PAN**	**CareStart *Pf*/*Pv***	**Total**
0 - 0.9%	16,549 (48.4)	5,303 (15.5)	3,924 (11.5)	8,436 (24.7)	34,212
1 -4.9%	8,436 (47.8)	1,073 (16.9)	1,833 (28.9)	408 (6.4)	6,344
5 - 39.9%	5,538 (68.2)	324 (4.0)	2,044 (25.2)	220 (2.7)	8,126
> 40%	1,209 (100)	0	0	0	1,209

5.3.2. Laboratory methods

Slides were labeled and air-dried horizontally in a covered slide tray in the school. Slides were stained with 3% Giemsa for 45 minutes at the nearest health facility at the end of each day. Blood smears of all RDT-positive children and an equivalent number of randomly selected blood slides from RDT-negative children were read at either the Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Programme laboratory in Kilifi or the Eastern and Southern Africa Centre of International Parasite Control (ESACIPAC)/KEMRI laboratory in Nairobi depending on the availability and workload of microscopists in each laboratory. Parasite densities were determined from thick blood smears by counting the number of asexual parasites per 200 white blood cells (or per 500 if the count was less than 10 parasites/200 white cells), assuming a white blood cell count of 8,000/μL. A smear was considered negative after reviewing 100 high-powered fields. Thin blood smears were reviewed for species identification. Two independent microscopists read the slides, with a third microscopist resolving discrepant results. A total of 612 (10.2%) slides had to be re-stained before a third reading was done due to poor quality staining. The poorly stained slides were immersed in xylene to remove oil immersion and then discolored using acetone and then re-stained with 3% Giemsa stain for 45 minutes.

5.3.3. Diagnostic performance of RDTs among individuals

The diagnostic performance of the three different RDTs, OptiMal-IT, Paracheck-Pf device and Paracheck-Pf dipstick, in detecting infection among individuals was compared to the assumed gold standard of expert microscopy, which is the approach commonly adopted by national malaria control programmes. At the individual-level, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and false positive rates (FPR), as well as their 95% confidence intervals, were calculated using the *diagt* command in Stata version 11.0 (Stata Corporation, College Station, TX, USA).

5.3.4. Classification of districts and schools using RDTs

Here, we compare the use of RDTs alone in classifying districts and schools according to specified prevalence categories against RDT results corrected by expert microscopy. Currently, the Kenya national malaria control programme categorizes districts into one of four malaria zones: stable transmission; seasonal transmission; epidemic-prone; and low risk[15]. Here we employ a slightly different classification based on prevalence of *Plasmodium* infection: < 1%, 1- 4.9%, 5 - 39% and ≥ 40%. These categories reflect underlying differences in the population dynamics and intensity of malaria transmission useful for selecting control strategies[16, 17] and the mix of interventions estimated to have maximal impact[17, 18]. Such control-related endemicity classifications are important for malaria control programmes since they determine the expected impact of intervention (due to the underlying basic reproductive number) and influence the choice of control interventions. For example in areas where infection prevalence is $\geq 40\%$, studies suggest that a combination of universal coverage with ITNs and complementary control interventions is necessary to interrupt transmission[17] while in areas of low transmission settings a single intervention strategy may suffice. For simplicity, we assume that the schools surveyed in each district provide a representative sample to estimate prevalence in each district, and that district-level prevalence is calculated as follows: total number of children found to be positive in the district / total number children examined in the district. On this basis, sensitivity was calculated as the percentage of districts in a given prevalence category which were correctly classified as such, while specificity was calculated as the proportion of districts not in a given prevalence category correctly classified as such. PPV was calculated as the proportion of districts in a given category by RDTs which were correctly identified, and NPV was calculated as the proportion of districts not to be in a given category by RDTs which were correctly identified as such. Ninety five percent exact binomial confidence intervals (CIs) were calculated.

The performance of RDTs at the school-level was first investigated by plotting a cumulative plot of school prevalences based on RDTs alone and on microscopy-corrected results. Sensitivity, specificity, PPV and NPV at the school-level were calculated on the same basis as the district-level analysis.

5.3.5. Cost analysis of alternative diagnostic strategies

Six alternative diagnostic methods were evaluated, including: (i) use of RDTs alone; (ii) expert microscopy alone; (iii) slide-corrected RDT results, based on microscopy of all RDT-positive results and an equal sample of RDT negatives; (iv) PCR-corrected RDT results, based on PCR of all RDT-positive results and an equal sample of the RDT negatives; v) RDT and expert microscopy of all samples; and vi) RDT and PCR of all samples.

The financial costs associated with the RDT and microscopy diagnostic strategies were based on our experience of conducting the school surveys in Kenya, whilst PCR costs were estimated based on the assumption that outsourcing PCR reading would cost USD 5 per sample examined (Drakeley C, personal communication). In estimating the costs of microscopy it was assumed that 18% of the slide readings would be discrepant and therefore need to be examined by a third reader as was observed in the present study. For the PCR-corrected RDT approach, it was assumed that all RDT positive samples would be examined individually using PCR, while the RDT negative samples would be combined into pools of five samples to help reduce costs[19]. For simplicity the costs of RDTs were based on the average cost of Paracheck-Pf RDTs (USD 1.40) from our procuring experience during the school surveys. To calculate the costs associated with PCR-corrected RDT and RDT plus PCR for all samples, we adopted a conservative estimate of RDT sensitivity (80%) and specificity (60%) estimates, based on results from published studies that have compared Paracheck-Pf RDTs and PCR[20, 21]. The number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) at different levels of infection prevalence were calculated as follows: TP=$SepN$, where Se is the sensitivity, p is prevalence, and N is the number of children per school; number of false positives (FP)=$(1-Sp)(1-p)N$, where Sp is specificity; the number of true negatives(TN)=$(1-Se)SpN$; number of false negatives (FN)=$(1-p)SpN$. As a simplification, we assume that a sample of 110 children per school would be included in the survey and the sensitivity and specificity remained constant at all prevalence levels. The costs of the microscopy-corrected RDT and PCR related diagnostic strategy are assumed to vary with the proportion of children who are RDT positive.

Relevant unit costs of the different diagnostic approaches were identified according to a standard ingredients based approach to costing[22]. The quantity and cost of each ingredient was identified from the project accounting systems and interviews with survey staff. Ingredient items were divided into staff, capital and consumables. Capital costs such as the costs of netbook computers and freezer, were annualized over the estimated useful life of the survey equipment using a discount rate of 3%, in line with WHO recommendations, (Table 5.2)[23]. Useful lives for the capital items were taken from either the WHO-CHOICE initiative estimates for Kenya or interviews with survey staff. To estimate the cost of the items per school, it was assumed that all capital items, with the exception of the freezer, would be used on a per team basis and each team would be able to visit 40 schools per term or survey phase. Hence, capital costs were divided across 40 schools. For the freezer, it was assumed that it could store samples from 200 schools and therefore the cost was divided across 200 schools. An average travel cost of 10,000 Kenya shillings (KES) (US$ 134.05) per day was assumed based on the cost of hiring a 10 seat vehicle for a day in Kenya in 2010. A 10% contingency allowance was also included. Costs were estimated in local currency and their current values were converted into equivalent US$ using an average exchange rate for the period between 1st September 2008 and 28th February 2010: KES 74.6 = US$1 (www.oanda.com). The unit costs are presented in Table 5.2, assuming 7.6% infection prevalence, as observed in this study using RDTs alone.

Table 5.2: Itemized cost of conducting school malaria surveys using alternative diagnostic methods Kenya, 2008 - 2010.The number of units and cost required for sampling 110 children in one school.

Item type	Unit	RDT only (Paracheck) Unit cost USD	Microscopy Unit cost USD	Microscopy-corrected RDTs[3] Unit cost USD	PCR-corrected RDTs[3] Unit cost USD
Equipment[1]	Dustbin	0.04	0.04	0.04	0.04
	Timer	0.23		0.23	0.23
	Cooler box	0.54		0.54	0.54
	Wooden drying rack		0.04	0.04	
	Staining jars		0.11	0.11	
	Measuring cylinder		0.04	0.04	
	Scissors				0.04
	Stapler				0.04
	Freezer				0.95
	Internet dongle	0.18	0.18	0.18	0.18
	Netbook computers	6.31	6.31	6.31	6.31
Salaries	Senior technician	67.02	67.02	67.02	67.02
	Technician	53.62	53.62	53.62	53.62
	Technician	53.62	53.62	53.62	53.62
	MoE officer	13.40	13.40	13.40	13.40
Training	1 day training	5.19	5.19	5.19	5.19
Consumables	Stationery	3.69	3.69	3.69	3.69
	Paracheck RDT	156.30		156.30	156.30
	Filter paper				15.06
	Blood lancet	2.95	2.95	2.95	2.95
	Sharps container	4.02	4.02	4.02	4.02
	Blood slides		5.31	5.31	
	Slide boxes		5.63	5.63	
	Buffer tablets		3.08	3.08	
	Distilled water		0.40	0.40	
	Giemsa stain		1.46	1.46	
	Kitchen rolls		1.14	1.14	
	Disposable gloves	3.35	3.35	3.35	3.35
	Cotton wool	0.25	0.25	0.25	0.25
	Methylated spirit	0.40	0.40	0.40	0.40
	Bin bags	0.27	0.27	0.27	0.27
	Paper towels	1.14	1.14	1.14	1.14

Table 5.2: continued

Item type	Unit	RDT only (Paracheck) Unit cost USD	Microscopy Unit cost USD	Microscopy-corrected RDTs[3] Unit cost USD	PCR-corrected RDTs[3] Unit cost USD
Consumables	Resealable bags				8.21
	Manilla paper				0.40
	Staples				0.30
	Questionnaires	13.40	13.40	13.40	13.40
Slide reading	Oil immersion		6.03	0.13	
	Lens tissue		2.95	0.06	
	Tally counters		0.04	0.04	
	Double slide reading		442.36	33.62	
	Third reading[2]		80.43	6.05	
	Printing costs		0.67	0.07	
PCR	Standard PCR				341.176
Transport & communica-tion	Car hire & driver	134.05	134.05	134.05	134.05
	Fuel & maintenance	40.21	40.21	40.21	40.21
	Airtime	5.36	5.36	5.36	5.36
	Supervision	35.25	35.25	35.25	35.25
Sub-total		**600.81**	**993.41**	**691.59**	**966.98**
Contingency (10%)		60.08	99.34	69.16	96.70
Total		**660.89**	**1,092.75**	**723.77**	**1,063.68**

[1]Capital costs assuming a 3% discount rate and that the items would be used over 200 schools
[2]Cost calculated assuming that 18% of the slides will have discordant readings.
[3]Cost calculated assuming that all RDT positive samples and equal number of RDT negative samples would be examined at 7.6% RDT *Plasmodium* prevalence.

5.4. Results

A total of 49,891 school children, aged 5 - 18 years, in 480 schools participated in the surveys[14]. Of these children, blood slides were examined using microscopy for 6,017 children: 3,117 children who were RDT-positive and 2,900 children who were RDT-negative. All slides were read twice, with 1,125 slides (18.7%) read by a third microscopist to resolve discrepancies and 612 (10.2%) slides re-stained due to poor initial staining in the field. Out of the 6,017 slides microscopically examined, 2,034 (33.8%) of slides were *Plasmodium* positive.

5.4.1. RDT performance at the individual level

The overall prevalence of *Plasmodium* infection on the basis of RDT results alone was 7.6% (95% CI, 6.3 - 8.9%) and was 4.3% (95% CI, 3.3 - 5.2%) by microscopy-corrected RDT results. Table 5.3 presents the diagnostic performance of RDTs, both overall and by RDT type. The overall sensitivity of RDTs alone was 96.1% (95% CI, 95.7 - 96.6%) and ranged from 94.9 - 96.3% according to RDT type. Overall specificity was 70.8% (95% CI, 69.7 - 72.0%). In terms of differences by RDT type, the Paracheck *Pf* device had the highest false positive rate (FPR) (31.2%) while OptiMal had the lowest FPR (22.6%). Overall, the PPV was 62.7%, with PPV lowest for Paracheck *Pf* dipstick (16.6%); while NPV overall was 96%. In total, 80 (1.3%) RDT readings yielded false negative results compared to microscopy; just over half (52.5%) of the false negatives had a parasite density of < 200 parasites/μL.

Table 5.3: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of alternative malaria rapid diagnostic tests compared to expert blood side microscopy during school malaria surveys in Kenya, 2008 - 2010. Ninety five percent confidence intervals are indicated in parenthesis.

RDT type	n[1]	RDT positive	Sensitivity	Specificity	PPV	NPV
All tests excluding CareStart	6,017	3,117	96.1 (95.6 - 96.6)	70.8 (69.7 - 72.0)	62.7 (61.5 - 63.9)	97.2 (96.8 - 97.7)
Paracheck *Pf* device	4,708	2,595	96.3 (95.7 - 96.8)	68.8 (67.5 - 70.1)	64.2 (62.9 - 65.6)	96.9 (96.4 - 97.4)
OptiMal	736	365	94.9 (93.3 - 96.5)	77.4 (74.4 - 80.5)	71.5 (68.3 - 74.8)	96.2 (94.9 - 97.6)
Paracheck *Pf* dipstick	573	157	96.3 (94.8 - 97.8)	76.0 (72.5 - 79.5)	16.6 (13.5 - 19.6)	99.8 (99.4 - 100)

[1] Number of children tested for malaria

5.4.2. Classification of districts and schools by prevalence class

Table 5.4 presents the proportion of districts correctly classified according to prevalence category based on RDT results compared to microscopy-corrected RDT results. Across all prevalence categories, 87.0% (60/69) districts were correctly classified by using results of RDTs alone. Correct classification was highest for districts in the < 1% and > 40% categories and lowest in the 1 - 4.9% category. Similarly, levels of sensitivity were highest in the < 1% and > 40% categories and lowest in the 1 - 4.9% category. Specificity was consistency high across all prevalence categories. The occurrence of false negatives (estimated as 1-sensitivity) was greatest in the 1 - 4.9% and 5 - 39.9% categories while false positives were highest in the 5 - 39.9% category.

Table 5.4: Proportion of districts correctly classified by rapid diagnostic tests (RDTs) compared to microscopy-corrected RDT results, according to prevalence category in school malaria surveys in Kenya, 2008 - 2010. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the RDTs are shown with their 95% confidence intervals (95% CI) in parenthesis.

***Plasmodium* prevalence category**	**Districts correctly classified**	**RDT sensitivity (95% CI)**	**RDT specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
0 - 0.9%	42/44 (95.5)	95.5 (90.5 - 100)	100 (100 - 100)	100 (100 - 100)	92.6 (86.4 - 98.8)
1 - 4.9%	5/10 (50.0)	50.0 (38.5 - 61.8)	96.6 (92.3 - 100)	71.4 (60.8 - 82.1)	91.9 (85.5 - 98.4)
5 - 39.9%	11/13 (84.6)	84.6 (76.1 - 93.1)	91.1 (84.3 - 97.8)	68.8 (57.8 - 79.7)	96.2 (91.7 - 100)
> 40%	2/2 (100)	100 (100 - 100)	97.0 (93.0 - 100)	50.0 (38.2 - 61.8)	100 (100 - 100)

Figure 5.1 presents estimated *Plasmodium* infection prevalence in each school based on RDT results alone and on microscopy-corrected RDTs results. RDT-based *Plasmodium* infection prevalence was systematically higher than microscopy-corrected RDT prevalence. The degree of over-estimation is greatest in high prevalence schools, where estimates based on the different diagnostic approach span different prevalence categories. In 11 schools, estimated RDT-based *Plasmodium* prevalence was lower than estimates of prevalence based on microscopy-corrected RDT results. Overall, 81.6% of schools were correctly classified by RDTs (Table 5.5).

Figure 5.1: Association between school level microscopy-corrected RDT prevalence and RDT only prevalence in school malaria surveys in Kenya, 2008 - 2010. The black solid line indicates the microscopy-corrected RDT prevalence and the horizontal gray bars indicate the RDT only prevalence. Vertical dashed lines represent the prevalence classes (0 - 0.9%, 1 - 4.9%, 5 - 39.9% and > 40%).

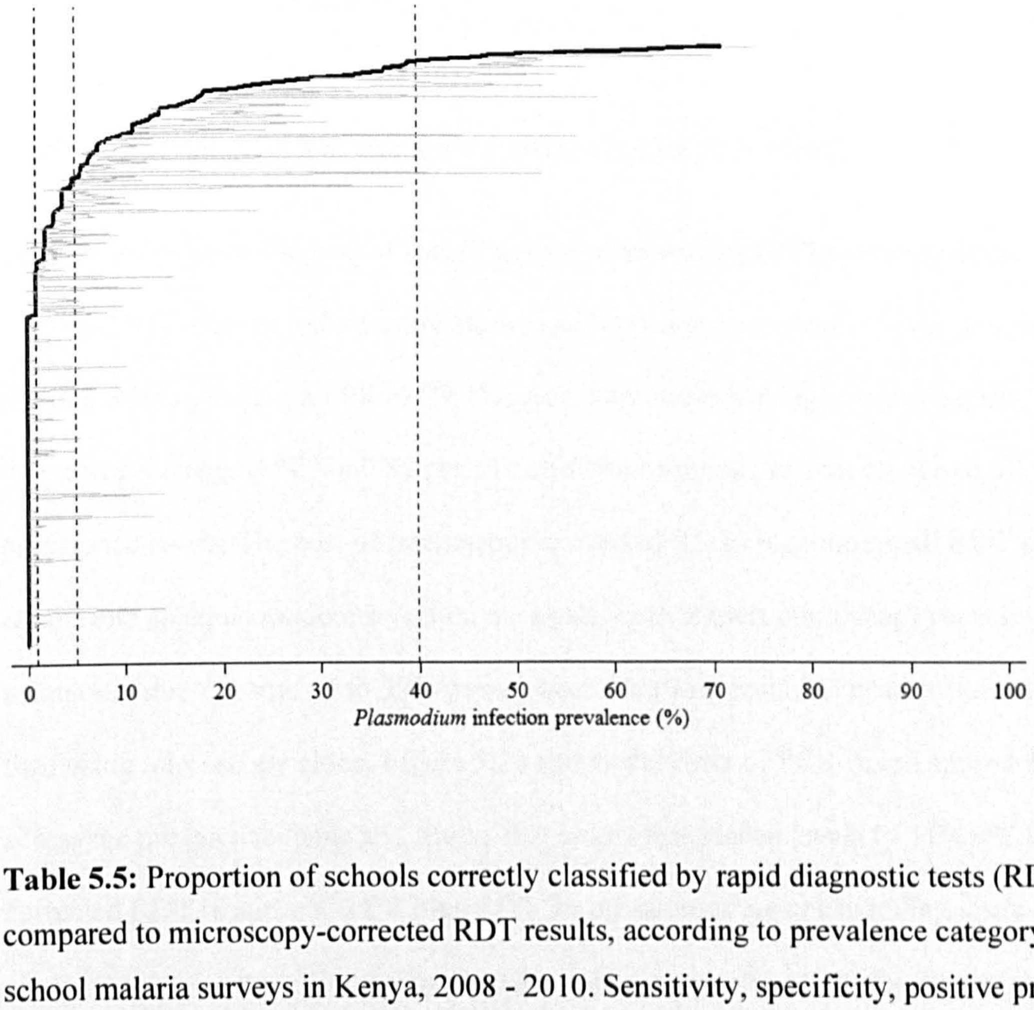


Table 5.5: Proportion of schools correctly classified by rapid diagnostic tests (RDTs) compared to microscopy-corrected RDT results, according to prevalence category in school malaria surveys in Kenya, 2008 - 2010. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the RDTs are shown with their 95% confidence intervals (95% CI) in parenthesis.

***Plasmodium* prevalence category**	**Schools classified by RDT**	**RDT sensitivity (95% CI)**	**RDT specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
0 - 0.9%	213/246 (86.6)	86.6 (83.2 - 90.0)	97.9 (96.4 - 99.3)	98.6 (97.4 - 99.8)	80.6 (76.6 - 84.5)
1 - 4.9%	31/56 (55.4)	55.4 (50.4 - 60.3)	94.2 (91.9 - 96.6)	62.0 (57.2 - 66.8)	92.6 (89.9 - 95.2)
5 - 39.9%	60/73 (82.8)	82.2 (78.4 - 86.0)	88.5 (85.3 - 91.7)	62.5 (57.7 - 67.3)	95.5 (93.5 - 97.6)
> 40%	11/11 (100)	100 (100 - 100)	96.5 (94.7 - 98.4)	45.8 (40.9 - 50.8)	100 (100 - 100)

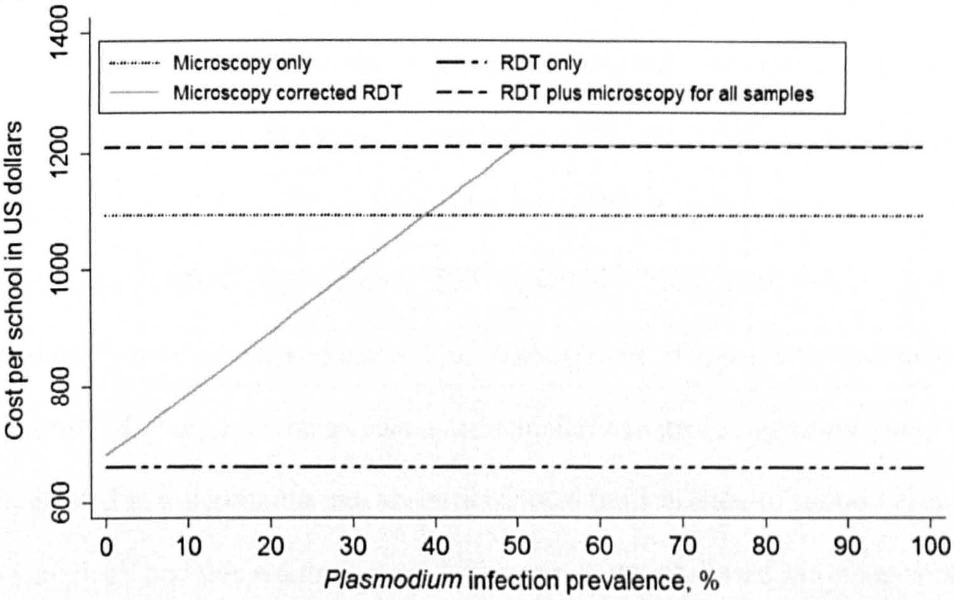
Importantly, in terms of identifying schools with high (> 40%) prevalence, 100% (11/11) of schools were classified correctly. Consistent with the district-level results, correct classification was worst in the 1 - 4.9% prevalence category. The false negative rate (1-sensitivity) was zero in the > 40% category and next lowest in the < 1% category; it was highest in the 1 - 4.9% category.

5.4.3. Cost implications of using alternative diagnostic methods.

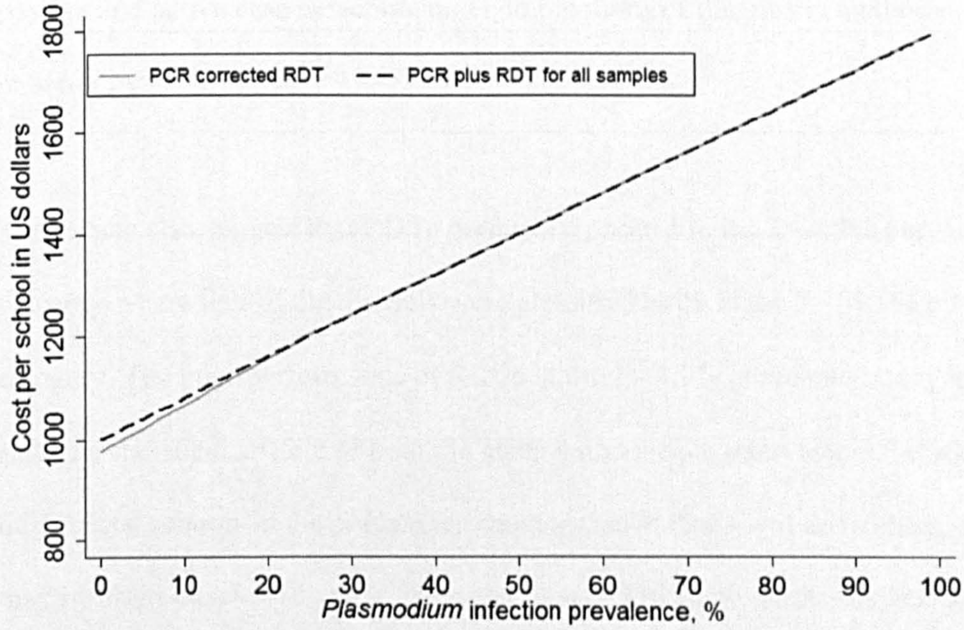
Figure 5.2a presents the cost of surveying one school using RDTs alone, microscopy-corrected RDT results, microscopy alone, and RDT and microscopy on all samples. Despite RDTs yielding a FPR of 29.2%, they were, unsurprisingly, the cheapest diagnostic strategy (USD 660.89 per 110 children sampled per school) across all prevalence levels. The cost of microscopy-corrected RDTs (examining all RDT positive results and an equal random selection of negatives by expert microscopy) was lower than using only microscopy, up to 39% prevalence. After this point, it became more expensive than using microscopy alone. Figure 5.2b shows the costs of PCR-based approaches across the prevalence range and shows that at low prevalence levels (< 11%) PCR-corrected RDT results and PCR plus RDT for all samples are cheaper diagnostic approaches than using microscopy only and microscopy plus RDTs for all samples.

Figure 5.2: The relationship between surveys costs and prevalence of *Plasmodium* infection according to (a) alternative microscopy and RDT approaches and (b) alternative PCR plus RDT approaches , during school malaria surveys in Kenya, 2008 - 2010 [14]. The RDT costs are based on the cost of Paracheck *Pf* device.

(a)



(b)



5.5. Discussion

The usefulness of malaria RDTs to estimate the prevalence of *Plasmodium* infection in malariometric surveys will depend on their diagnostic performance, ability to correctly classify localities according to intensity of malaria transmission, and their costs relative to other diagnostic approaches. At the individual level, the current study found RDTs to have a sensitivity of 96.1% and a specificity of 70.8%, which is consistent with previous studies conducted among school-aged children[24, 25]. In terms of classifying localities according to infection prevalence, RDTs used in school-based surveys performed well in defining where prevalence was < 1%, characteristic of areas with low stable endemic control[26]. In very low transmission areas malaria control programmes may be more interested in ascertaining true absence of local transmission to support elimination strategies[27] and this would require different population-based sampling strategies such as passive and active case detection, and combinations of diagnostic methods such as PCR or serology.

The results also suggest that RDTs performed poorest in the 1 - 4.9% prevalence category where half of the districts were classified to be in the 5 - 39.9% prevalence category. The poor performance of RDTs in the 1 - 4.9% prevalence category, may reflect a statistical artifact of both the narrow prevalence interval and the small numbers of districts/ schools in the prevalence category, such that slight differences in prevalence may result in misclassification. However in such low to moderate transmission settings that characterize most of east and southern Africa[28], the results suggest that correction of RDT results using pooled PCR is cheaper than using microscopy as is routinely done in population-based surveys in these regions[29]. The use of RDTs to detect infection and pooled PCR to validate infection status has been used in various field based surveys including the 2010 malaria indicator survey (MIS) in Swaziland[30, 31] and has been shown to be reliable in detecting infections and cost saving[19, 32, 33]. In the 2010 Swaziland MIS, where the overall prevalence by RDTs was 0.2%, PCR pools of 25 samples each were used and only 2 out of 162 pools tested positive, thereby greatly reducing diagnostic costs (by over 95%) and providing reliable prevalence estimates[31]. In a cohort study of Ugandan children in a low endemicity setting, pools of 49 samples resulted in 95% cost and labour savings in settings where prevalence was 0.01%[32]. The optimal pool sizes required to balance between cost saving and accuracy are likely to depend on the underlying prevalence of infection[34]. In high prevalence settings, the current results indicate that correction of RDT results using PCR is at least twice more expensive than using RDTs alone. To reduce costs, lot quality assurance sampling (LQAS) may help reduce required sample sizes; for example, a study in Malawi on the utility of LQAS in estimating mosquito net use found that LQAS provided similar estimates as the standard MIS, but at lower cost[35]. The use of LQAS has previously been used for estimating the prevalence of *Schistosoma mansoni* infection in order to target mass treatment[36-38]. A major limitation of LQAS surveys is that they do not provide precise estimates of prevalence rather classify schools/communities into predefined categories of infection prevalence[39].

This study has several limitations. First, RDT performance was compared with microscopy and only a sample of the RDT negative slides were examined. The presence of sub-microscopic infections when microscopy is used as the comparator may result in false positives as a result of infections below the threshold of detection by microscopy[40, 41]. Recent studies have highlighted the extent of sub-microscopic infections, indicating that microscopy misses over half of the infections detected through PCR[42, 43]. This could lead to an under-estimation of RDT performance due to sub-microscopic infections commonly harbored by school age children[43]. Persistent antigenaemia in HRP-2 based

RDTs has also been suggested as the cause false positivity after treatment or after a recent resolved illness[10, 40, 44-47]. In the absence of a reliable 'gold standard' such as PCR to validate the RDT results, statistical methods such as latent class models may be useful in estimating the diagnostic performance[48]. A second limitation is that the cost analysis did not allow for sensitivity and specificity of RDTs to vary with infection prevalence and RDT type, whereas it is known that the performance of RDTs crucially depends on the underlying prevalence[49] and the type of RDT used[50], and such variation may cause an underestimation of costs associated with the different diagnostic strategies. Thirdly, the cost estimates were based on a conservative RDT performance of 80% sensitivity and 60% specificity, which is lower than what has been observed by the WHO-FIND malaria diagnostics programme[50] for most of the commonly used RDTs and therefore the costs of re-examining misclassified samples may have been overestimated. Further to the misclassification due to poor diagnostic performance, school-based surveillance has a number of limitations, including differentials in enrolment, absenteeism, types of schools sampled and the ages of children sampled [13, 14], which may produce different prevalence estimates compared to community-based surveillance.

A striking implication of the current results is the poor performance of microscopy, even in the hands of well trained technologists with adequate quality assurance, critically depends on the quality of slide preparation and storage[51, 52]. It was noteworthy that 10.2% of slides required re-staining and that 18.7% of slide readings were discrepant between microscopists. The technical difficulties of microscopy should not be under-estimated. During MISs conducted during 2009 in the Republic of Sudan, South Sudan and Namibia both blood slides and RDTs were collected but it was found that slides were so poorly stained or stored and microscopy was ultimately abandoned (Snow RW and Noor AM, unpublished data). In addition to the reasonable performance of RDTs in classifying localities and their low cost, RDTs offer real technical advantages for point-of-care diagnosis and immediate treatment during surveys.

This chapter indicated that RDTs represent a cheap diagnostic approach in school malariometric surveys and can be used to reliably estimate infection prevalence at very low and high prevalence categories. The results also demonstrate that RDTs were least specific at moderate transmission settings but at such transmission levels, RDTs in combination with more accurate diagnostic tools such as pooled PCR still offered an affordable alternative. In addition to schools providing an inexpensive approach to estimate malaria infection prevalence, school-based surveys can also be used to monitor ITN use by school children and their families. However the use of schools to monitor ITN coverage is predicated on the assumption that school children can reliably report their own and others' net use. To assess the usefulness of school surveys in monitoring bed net coverage, the next chapter evaluates the congruence between reports of net use from school-based surveys and reports from household-based surveys.

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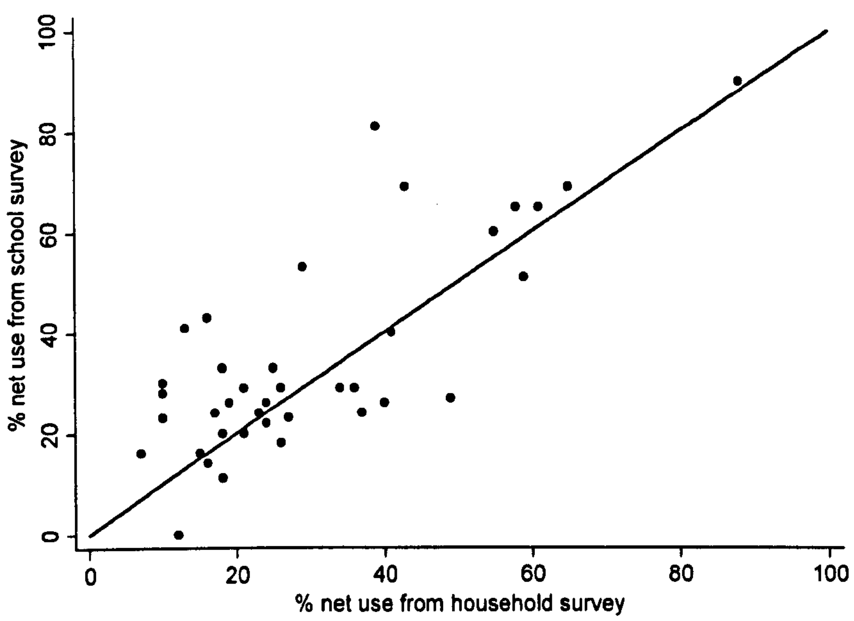
Chapter 6 : Congruence between school children's reports of household ownership and use of mosquito nets and reports from household surveys in two settings in Kenya

6.1. Introduction

Chapter 2 reports results from a nationwide school malaria survey and provides important information on the epidemiology and disease burden of malaria in school children. In this thesis, I have proposed that school malaria surveys provide a rapid and inexpensive approach to malaria surveillance complementary to household-based malaria surveys[1,2]. The previous chapter demonstrated that the use of RDTs in schools can reliably estimate malaria endemicity based on *Plasmodium* infection prevalence among school children, especially at low and high prevalence. This chapter investigates whether reports by school children provide a reliable indicator of bed net coverage in the wider community. In this chapter I oversaw the data collection in the Tana River studies and I analysed the data presented in this chapter. The school and community surveys in Kisii and Rachuonyo were conducted by Jennifer Stevenson and colleagues from LSHTM and KEMRI/CDC.

A previous study in Uganda compared school children's reports of household use of bed nets as monitored by teachers through a questionnaire against estimates of net use based on household surveys[3]. There was a high correlation between school children's reports of household ownership of ITNs (Pearson's correlation=0.82) and untreated nets (Pearson's correlation=0.77) (Figure 6.1). Reporting by school children has also been shown to be a reliable indicator in other disease control programmes. For example, school children's reports been shown to be reliable proxy measure of population coverage of ivermectin coverage in onchocerciasis control programmes[4, 5]. In schisotosmiasis control programmes, self-reporting of blood urine by school children has been demonstrated in multiple settings to be a reliable indicator of the prevalence of *Schistosoma haematobium*, and thus identify areas that require mass treatment with praziquantel[6-8].

Figure 6.1: Relationship between estimates of household use of any net reported by school children and estimates obtained from household-based surveys in Uganda, 2005. Pearson's correlation= 0.77. Adapted from ref[3].



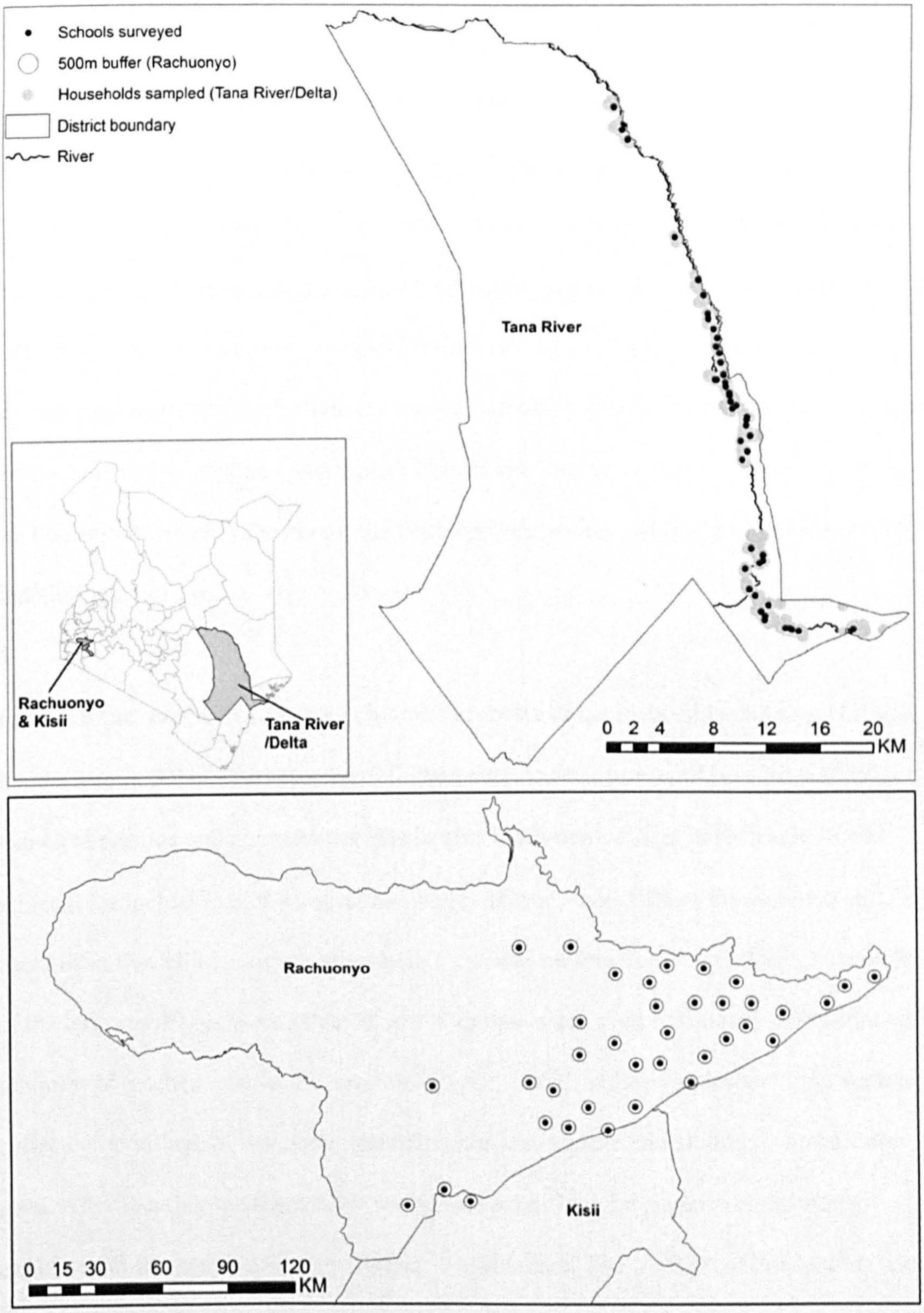
The aim of this chapter is to evaluate the congruence between school children's reports household ownership of nets and their own use of nets (as assessed through school surveys) and reports of net ownership and use from household-based surveys. A secondary aim is to assess the difference in estimates of net coverage at sub-national (province) levels in Kenya.

6.2. Methods

The analysis in this chapter uses data from paired school-community surveys conducted in Tana River and Tana Delta districts, coastal Kenya in 2009 and in Kisii and Rachuonyo districts in the western highlands in 2010, shown in Figure 6.2. The data from Tana River and Tana Delta form the baseline survey of the cluster randomised trial described in Chapter 4. The school and household surveys in Kisii and Rachuonyo were conducted by Jennifer Stevenson and colleagues from LSHTM and KEMRI/CDC. In both settings, a standardised protocol was employed in the school surveys and household surveys were based on the design of malaria indicator surveys.

Additionally, province-level estimates of net use from the nationwide school surveys described in Chapter 2 are compared with estimates from national sample household surveys conducted in Kenya between 2007 and 2010.

Figure 6.2: The geographical distribution of the schools and households in the paired school and household surveys in Tana River/Delta and Kisii/Rachuonyo conducted in 2009 and 2010, respectively. Insert: A map of Kenya showing Tana River, Tana Delta, Kisii and Rachuonyo districts.



6.2.1. Tana River/Delta school and household surveys

The school surveys in Tana River and Tana Delta districts are described in detail in Chapter 4. In these surveys, 49 schools were sampled for the baseline survey in February 2009. In each of the selected schools, 110 children, 11 boys and 11 girls from classes 2-6, were randomly selected using computer-generated random number tables. A questionnaire was administered to the selected children, which collected demographic data on age, sex, parent/ guardian's name and village of residence. Data were also collected on socio-economic variables, child's net use and household net ownership and use, net characteristics such when the net was obtained, whether it was treated or not, and from where it was obtained. Additional information on the number of nets available in the household, whether the house had been sprayed with an indoor residual spray (IRS) and siblings' net use was also collected.

To assess the reliability of school children's reports of net ownership and use, children sampled in the school survey were followed back to their households in May 2009. For logistical reasons and convenience, the largest catchment village in each school was selected for inclusion in the household survey if more than 50% of the sampled children came from that village. In schools where there was no one dominant village, two or three of the largest villages were selected until a sample size of approximately 50 children per school was reached. To locate each child's household, village guides and information collected on village of residence, parent's/guardian's name and siblings' names were used. After locating the household, household heads had the purpose of the study explained to them and informed consent was obtained. The location of households was determined using a Garmin eTrex global positioning system (Garmin, Olathe, Kansas, USA).

A questionnaire was administered to household heads which collected information on the household head's name and age, household construction, household head's level of education, household head's occupation, ownership of livestock and household items among others, and availability of nets in the household. Data were also collected on net ownership and use among all household members and school enrolment of children. All reported nets were visually inspected to ascertain use and treatment status. Data were collected using HP iPAQ 114 handheld personal digital assistants (PDAs). The data collected from households were used to assess the individual-level reliability of school children's report and the congruence between school- and cluster-level estimates of net ownership and use.

6.2.2. Kisii / Rachuonyo school and household surveys

The Kisii and Rachuonyo surveys were part of a study assessing the impact of ITNs and indoor residual spraying (IRS) on malaria in the highland and epidemic prone districts in Kenya. The school surveys were conducted in 37 schools in areas lying between 1400 and 1600m in Kisii and Rachuonyo districts in July 2010. The same standard protocol described in Chapters 2 and 4 was used in these surveys. A total of 110 children, 11 boys and 11 girls from classes 2-6, were randomly selected in each school using computer-generated random number tables. Using a questionnaire, data were collected on age, sex, parent's name, and closest market to their residence, ownership of basic household assets, net use and IRS.

All the children included in the school surveys were subsequently followed to their households using the information collected during the school survey in order to assess the individual-level reliability of school children's reports. With the help of village guides, the homes of the children included in the school surveys were located and the same questionnaire as used in the school survey was administered on using PDAs.

Ethical approval for the surveys was obtained from the Kenya Medical Research Institute and National Ethics Review Committee. In the school surveys, individual assent was obtained from each child before the survey while in the household surveys, consent was sought for adults (those of 18 years of age and above) and from parents for children up to 13 years of age. Assent was obtained for those aged 13 to 17 years accompanied by parental consent.

Additional household surveys were conducted immediately after the school surveys in July 2010 in order to assess the congruence between school-level estimates and cluster-level estimates, as assessed by household surveys. All houses within 500m of the sampled schools were mapped and enumerated, with only houses within an altitude range of 1400-1600m included in the survey. From the sampled households, approximately 12-15 compounds (a compound was defined as a collection of households mainly belonging to members of the same extended family) were randomly selected for inclusion in the survey. All people aged above 6 months in the sampled compounds were included in the survey. After obtaining informed consent from the household heads data were collected on household construction and household assets, use of anti-malarial measures (recent IRS activities, net ownership and use, use of mosquito coils, sprays etc.), recent fever episodes, treatment seeking behaviour and travel history

6.2.3. Province and national comparisons

Congruence between estimates derived from school surveys and household survey was further assessed at national and provincial levels by comparing estimates of net use from the schools surveys described in Chapter 2 and three national sample household surveys conducted in Kenya between 2008 and 2010 [9]. The household surveys included the 2010 Kenya Malaria Indicator Survey (KMIS 2010)[10], the 2009 FinAccess survey by the Kenya Financial Sector Deepening programme (2009 FSD survey)[11] and the 2008-2009 Kenya demographic health survey (KDHS 2008-09)[12].

6.2.4. Data analysis

To estimate the proportion of reported net ownership and use, null random effects models were used adjusting for clustering at the school and household levels for the school-based and community based data respectively.

To assess the individual-level reliability of school children's report versus household reports, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated using the *diagtest* command in Stata.
Lin's concordance correlation coefficient for agreement[13] and the Bland and Altman method[14] were used to assess the congruence between estimates of net ownership and use at the school and cluster/community levels, based on school surveys and household surveys, respectively. In both the Tana River/Delta and Kisii/Rachuonyo surveys, schools were matched to their catchment clusters and the pairs of estimates compared. The Lin's concordance correlation measures the agreement between two continuous estimates, whilst the Bland and Altman method compares the pair-wise differences and the average of the estimates. Here, the mean difference (mean of school-based estimates

minus cluster-level estimates) and the corresponding 95% limits of agreement (mean difference +/- 1.96 standard deviations) are reported. To assess whether there was a statistically significant linear trend between the differences and the mean estimates from the school and household surveys, standard linear regression was used and a p-value<0.05 was considered significant.

To identify factors that influenced the magnitude of the difference between the estimates univariable and multivariable regression modelling was employed. In the Tana and Kisii/Rachuonyo data, factors such as the mean age of school children, location and household-level bed net coverage were assessed for their association with the observed difference between the school and household survey estimates. In the national sample surveys, factors such as malaria infection prevalence, malaria transmission zone, province and distance of the cluster from school were assessed.

6.3. Results

In the Tana River and Tana Delta school surveys, a total of 5,071 children in 49 schools were sampled. Of these children, 3,831 (74.9%) from 68 villages/clusters were selected to be followed to their households 3,241 children (63.9% of all children surveyed) were located during the household survey and for whom household survey data were collected. The main reasons for not locating children were that they lived across the river, their families had moved across the river for farming, or adults were absent during household visits, even after follow-up visits. Overall, data were collected on 19,595 individuals from 2,790 households.

In the Kisii/Rachuonyo surveys, a total of 3,932 children were sampled from 37 schools for the school survey and subsequently followed to their households. The majority of children (97%) were located in the households and data collected on bed net ownership and use. In addition, a total of 929 households located within 500m of the 37 schools were sampled and bed net data collected for 2,833 individuals.

6.3.1. Net ownership and use, as reported by school children and in household surveys

Estimates of net ownership and use from school and households surveys are presented in Table 6.1. In the Tana River/Delta school survey, 71.3% (95% CI: 65.6 – 76.9%) of children reported having nets, but only 67.3% (95% CI: 61.6 – 73.1%) reported using a net the night before the survey. These estimates were higher than those reported in the household surveys: in the 5-14 years age group, 47.8% (95% CI: 41.5 – 54.0%) of children were reported to have nets and only 45.8% (95% CI: 39.7 – 52.0%) were reported to use a net the night before the survey.

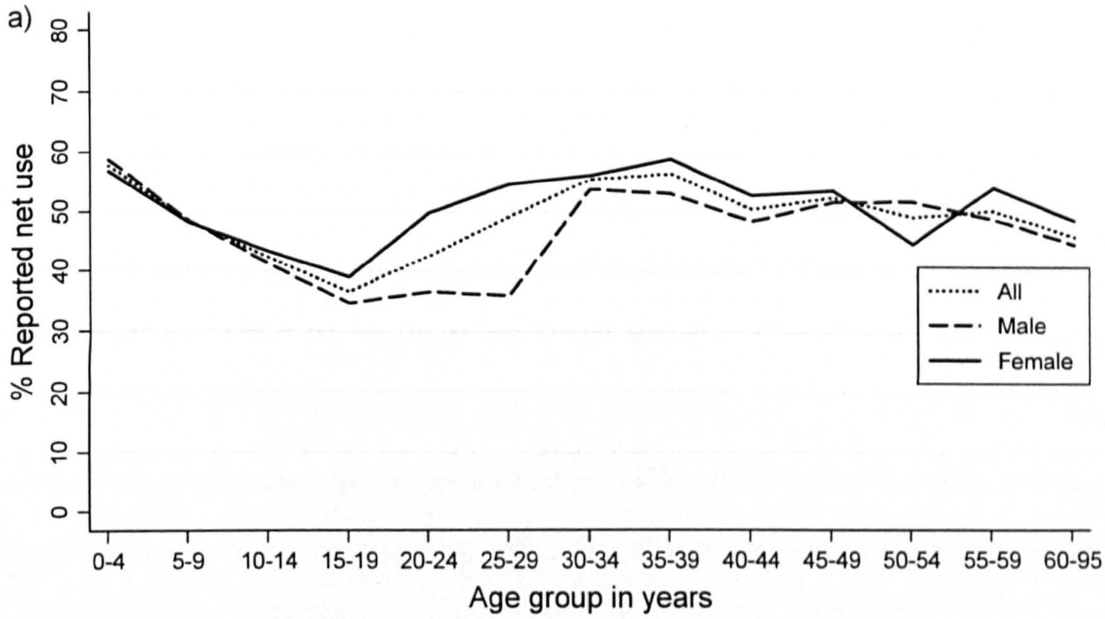
In the Kisii/Rachuonyo surveys, 51.9% (95% CI: 47.6 – 56.1%) of school children reported having nets and 47.5% (95% CI: 43.4 – 51.6) reported sleeping under a net the night before the survey. In contrast to the Tana surveys, the net use estimates from school children's reports and those obtained during household surveys were similar (the confidence intervals overlap): 47.5% (95% CI: 43.4 – 51.6) vs. 44.8% (95% CI: 40.3 – 49.3). In both household surveys, school-aged children were least likely to use nets, Table 6.1 and Figure 6.3a and 6.3b.

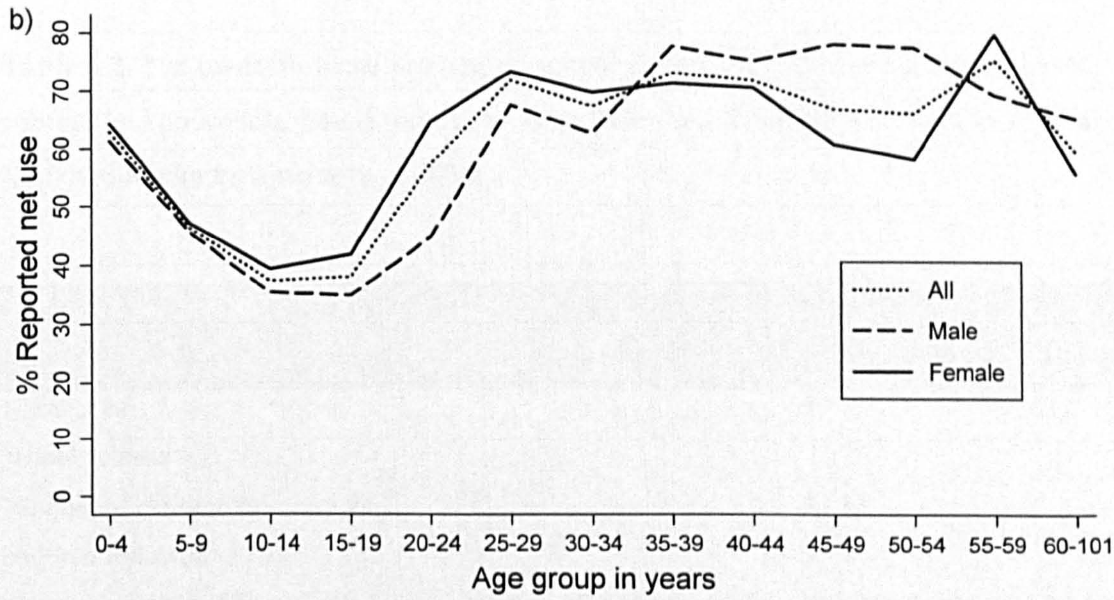
Table 6.1: Estimates of net ownership and use, based on school children's report and from household surveys in northeast and western highland Kenya, 2008-2010.

	Survey dates	n, schools/ clusters	n, children / persons all ages	Net ownership all ages, %(95% CI)[1]	Net use all ages, %(95% CI)[1]	n, children 5-14 yrs	Net ownership 5-14 yrs, %(95% CI)[1]	Net use 5-14yrs, %(95% CI)[1]
Tana River and Tana Delta								
School survey	February – March 2009	49	5,071	-	-	5,071	71.3 (65.6 – 76.9)	67.3 (61.6 – 73.1)
Household survey	May 2009	68	19,485	50.3 (44.2 – 56.4)	47.8 (42.0 – 53.6)	8,090	47.8 (41.5 – 54.0)	45.8 (39.7 – 52.0)
Kisii and Rachuonyo								
School survey	July 2010	37	3,829	-	-	3,829	51.9 (47.6 – 56.1)	47.5 (43.4 – 51.6)
Household survey	July 2010	37	2,833	-	57.1 (54.2 – 59.9)	749	-	44.8 (40.3 – 49.3)

[1] In the Tana school surveys, children were asked about their siblings' net ownership and use. The estimates are reported as the siblings data.
[2] Proportions and 95% confidence intervals estimated using a multilevel random effects model adjusting for clustering at the school level in the school surveys, and at the household level in the household surveys. In the national sample household surveys, the mean of the cluster level means and confidence intervals are reported.

Figure 6.3: Proportion of the population sleeping under any net the night before the survey: **a)** Reported net use by age in the 2009 Tana River/Delta districts household survey, and **b)** Reported net use by age in the 2010 Kisii and Rachuonyo districts household survey.





6.3.2. Reliability of individual net reports

Of the 3,241 children followed to their households in the Tana River/Delta school survey, 71.0% reported owning a net in the school surveys, but only 47.8% were reported to own a net in the household survey (Table 6.2). In the school survey, 67.6% of children reported sleeping under a net the night before the survey while only 46.2% were reported to have slept under a net the night before the survey in the household survey. Of the 3,832 children followed to their households in the Kisii and Rachuonyo school surveys, 51.7% reported owning nets in the school survey while only 34.3% were reported to own nets in the household-based surveys. In the school surveys, 47.3% of children reported sleeping under a net the night before the survey while only 30.6% of the children were reported to have slept under a net the night before the survey in the household-based survey.

Table 6.2: Net ownership and use among school children reported using school-based surveys and household-based surveys in Tana River and Tana Delta surveys in 2009 and Kisii and Rachuonyo surveys in 2010.

	Tana school surveys[1]	Tana HH surveys[1,2]	Kisii/Rachuonyo school surveys	Kisii/Rachuonyo HH surveys
Number of schools/clusters	49	68	37	37[1]
Number of children of children followed to HH	3,241		3,832	
Net own, % (95% CI)	71.3 (65.6 – 76.9)	47.8 (41.2 - 54.3)	51.7 (50.0 – 53.3)	34.3 (32.6 – 36.0)
Net use, % (95% CI)	67.6 (61.4 – 73.7)	45.9 (39.7-52.0)	47.3 (45.6 – 48.9)	30.6(28.9 – 32.2)

[1] Based on catchments
[2] Estimates based on children between the ages of 5 and 14 years.

Table 6.3 reports the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of the school-based reports compared to the household surveys. Overall, children were more likely to report not having nets if they actually did not have nets in the household: sensitivity was 78.7% in Tana River and and 69.4% in Kisii/Rachuonyo. However, specificity was low both in the Tana River (40.6%) and Kisii/Rachuonyo surveys (56.1%).

Table 6.3: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of children's reports on bed net ownership and use in school-based surveys compared to reports from household-based surveys in Tana River and Tana Delta surveys in 2009 and Kisii and Rachuonyo surveys in 2010. Ninety five percent confidence intervals are indicated in parenthesis.

	Sensitivity	**Specificity**	**PPV**	**NPV**
Tana River/Delta				
Reported net ownership	78.7 (77.3 – 80.1)	40.6 (38.9 – 42.3)	54.9 (53.2 – 56.6)	67.4 (65.8 – 69.0)
Reported net use	75.7 (74.2 – 77.2)	43.7 (42.0 – 45.4)	53.7 (52.0 – 55.5)	67.6 (66.0 – 69.2)
Kisii/Rachuonyo surveys				
Reported net ownership	69.4 (68.0 – 70.9)	56.1 (54.6 – 57.7)	40.7 (39.2 – 42.3)	80.9 (79.6 – 82.1)
Reported net use	65.3 (63.8 – 66.8)	60.6 (59.1 – 62.2)	41.9 (40.3 – 43.5)	80.1 (78.8 – 81.4)

6.3.3. Congruence between school and cluster summary estimates

Figures 6.4 - 6.7 present the relationship between reported net use in the school and household surveys in the Tana River/Delta and the Kisii/Rachuonyo surveys. Figures 6.4 and 6.5 compare the reported net use estimates in the school surveys and net use estimates among children aged 5-14 years in the household surveys, while Figures 6.6 and 6.7 compares the reported net use estimates from the school surveys to the net use estimates among all ages in the household surveys.

6.3.3.1.Estimates for school-aged children

Overall, school surveys over-estimated net use compared to the household-based surveys in the Tana surveys among children between 5 and 14 years (Figure 6.4a and b). The Lin concordance correlation coefficient was 0.40 (95% CI: 0.24 – 0.56). The mean difference between reported net use in the school survey and the household survey was 21.57% (95% Limits of agreement (LOA): -15.51 to 58.65%) (Figure 6.4c). However, there was no statistical evidence of a linear association between the differences and average net use estimates from the Tana River/Delta school and household surveys (p=0.537).The school surveys underestimated net use in only 3/49 schools compared to the household-based survey (Figure 6.4b).

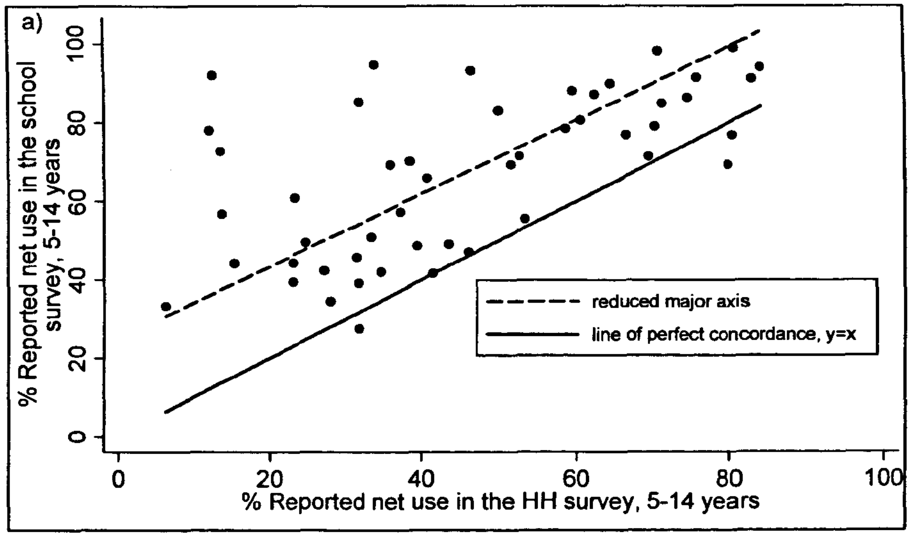
Similarly, in the Kisii and Rachuonyo surveys, the school survey overestimated net use compared to the household surveys in the majority of schools (23/37 schools), however the school surveys underestimated net use in areas where net use was high by household surveys (Figure 6.5a and 6.5b). The Lin concordance correlation coefficient was 0.39 (95% CI: 0.16 – 0.61). The mean difference (school estimates-household survey estimates) between the school and household estimates was 3.58% (range:-42.78 – 47.62%, SD: 21.2). However mean difference was associated with the average net use from the school and household surveys (Figure 6.5c). There was a 0.8 decrease (-0.80, 95% CI: -1.16 - -0.44) in the mean difference for every percentage increase in the average of the school and household surveys net use estimates (Figure 6.5c).

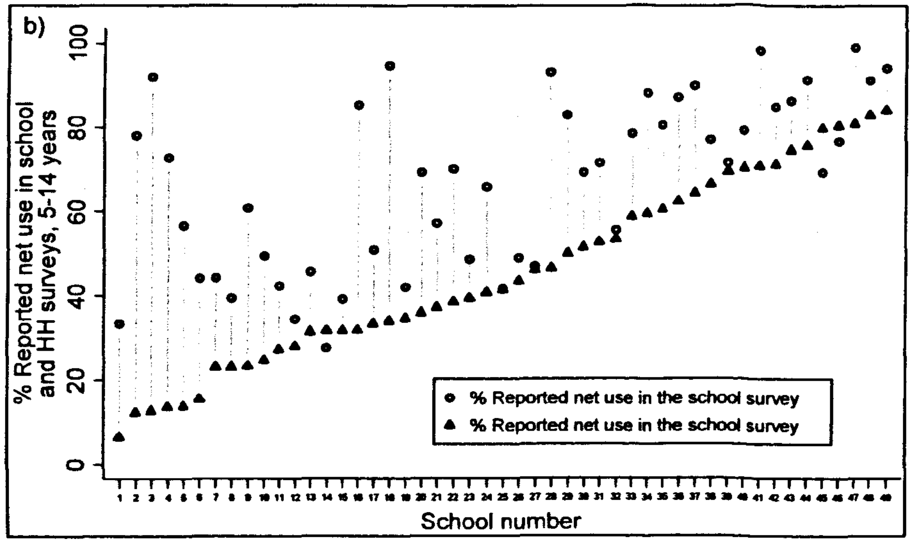
6.3.3.2. Estimates for all ages

Comparing the reported net use estimates from the school surveys to the household survey estimates among all ages, the school surveys overestimated net use in the Tana surveys (Figure 6.6a and 6.6b). The school surveys overestimated net use in 43/49 schools. The concordance correlation coefficient was 0.40 (95% CI: 0.24 – 0.57) indicating low agreement. The mean difference between reported net use in the school survey and reported net use among all ages in the household survey was 19.60 (95% Limits of agreement (LOA): -16.93 to 56.13%), (Figure 6.6c). There was no evidence of an association between the differences and the average of the school and household survey estimates, p=0.927.

In contrast, school children's net use estimates in the Kisii/Rachuonyo surveys were lower than net use estimates among all ages from the household surveys in majority of schools, 24/37 schools (Figures 6.7a and 6.7b). Concordance correlation coefficient was low, 0.35 (95% CI: 0.12 – 0.59). Overall the mean difference between the school and household estimates was -8.92 (range: -43.08 to 34.46, SD=17.96), however the mean difference was associated with the average of the school and household net use estimates (Figure 6.7c). There was a 0.56 decrease (95% CI: -0.96 to -0.16) in the mean difference for every percentage increase in the average of the school and household surveys net use estimates (Figure 6.7c).

Figure 6.4: Relationship between reported net use estimates from school surveys and net use estimates among school-age children (5-14 years) in the community from household-based surveys in Tana River and Tana Delta districts in Kenya in 2009. **a)** A scatter plot of the school and cluster level estimates. The dashed line represents the reduced major axis which shows the centre of the data. The solid diagonal line represents the line of perfect concordance, (y=x). **b)** A plot of the school and cluster level estimates with the solid vertical lines showing the magnitude of the differences between school and household estimates. **c)** Relationship between the difference (school estimates – HH estimates) and average reported net use estimates from school surveys and net use estimates among school-age children (5-14 years) in the community from household-based surveys. The solid line represents the mean and the dashed horizontal lines, difference and the 95% limits of agreement.





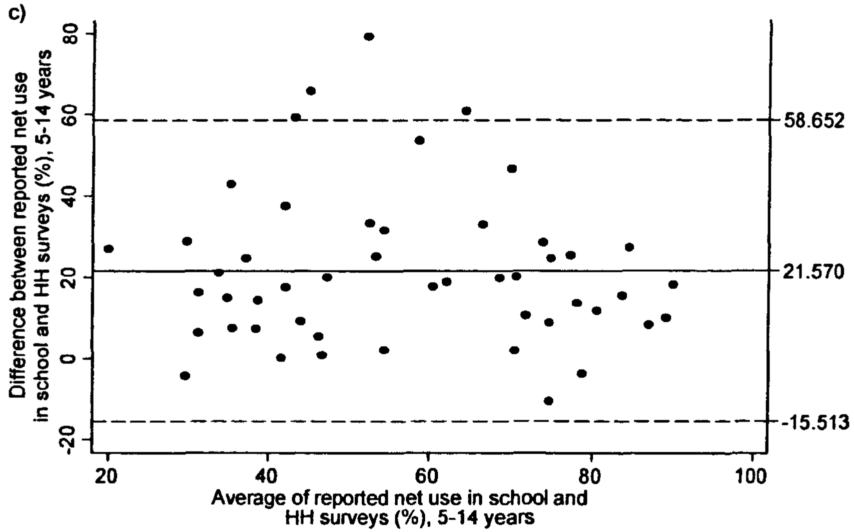
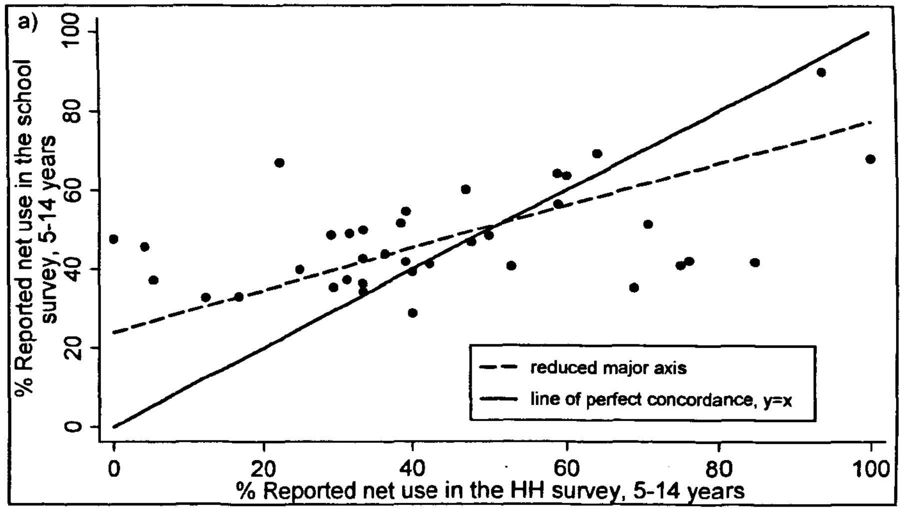
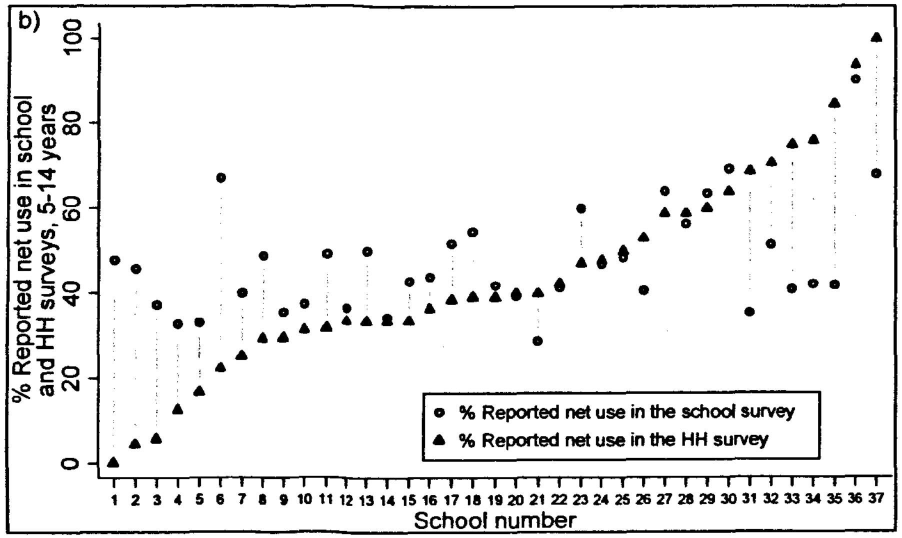


Figure 6.5: Relationship between reported net use estimates from school surveys and net use estimates among 5-14 year old children in the community from household-based surveys in Kisii and Rachuonyo districts in Kenya in 2010. **a)** A scatter plot of the school and cluster level estimates. The dashed line represents the reduced major axis which shows the centre of the data. The solid diagonal line represents the line of perfect concordance, (y=x). **b)** A plot of the school and cluster level estimates with the solid vertical lines showing the magnitude of the differences between school and household estimates. **c)** Relationship between the difference (school estimates – HH estimates) and average reported net use estimates from school surveys and net use estimates among school-age children (5-14 years) in the community from household-based surveys. The solid line represents the mean and the dashed horizontal lines, difference and the 95% limits of agreement.





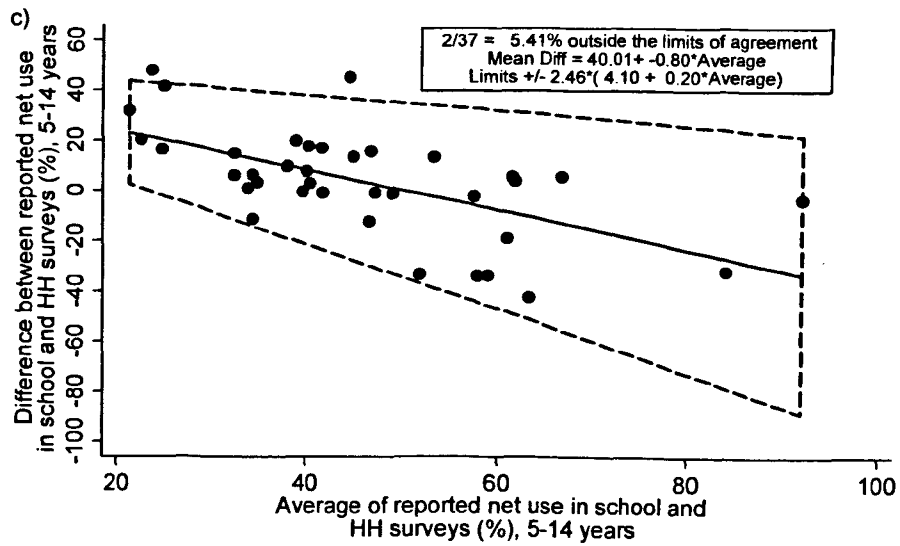
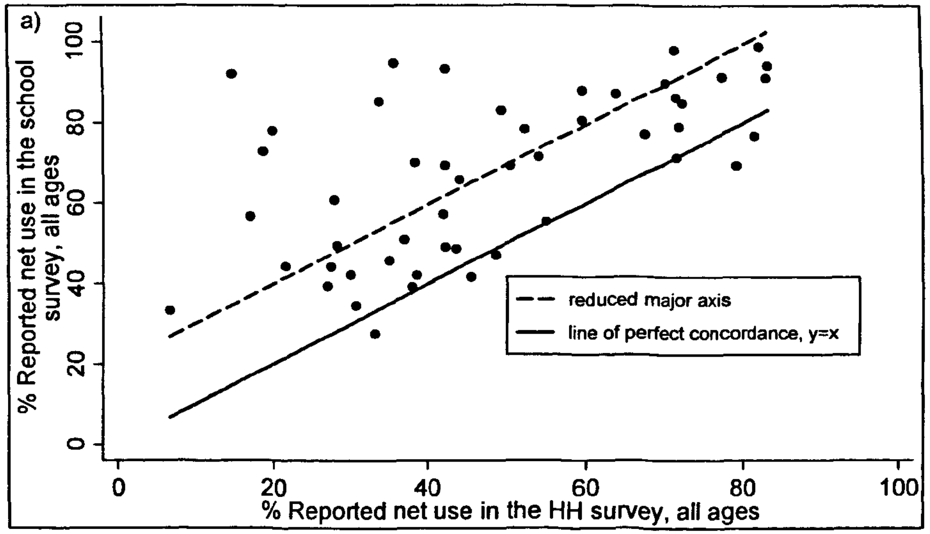
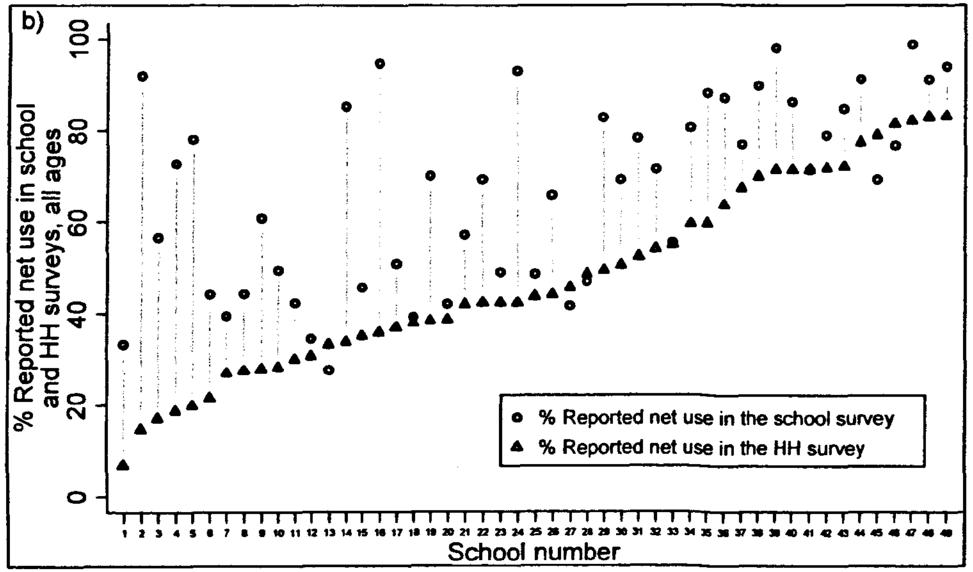


Figure 6.6: Relationship between reported net use estimates from school surveys and net use estimates in all ages in the community from household-based surveys in Tana River and Tana Delta districts in Kenya in 2009. **a)** A scatter plot of the school and cluster level estimates. The dashed line represents the reduced major axis which shows the centre of the data. The solid diagonal line represents the line of perfect concordance, (y=x). **b)** A plot of the school and cluster level estimates with the solid vertical lines showing the magnitude of the differences between school and household estimates. **c)** Relationship between the difference (school estimates – HH estimates) and average reported net use estimates from school surveys and net use estimates in the community from household-based surveys. The solid line represents the mean and the dashed horizontal lines, difference and the 95% limits of agreement.





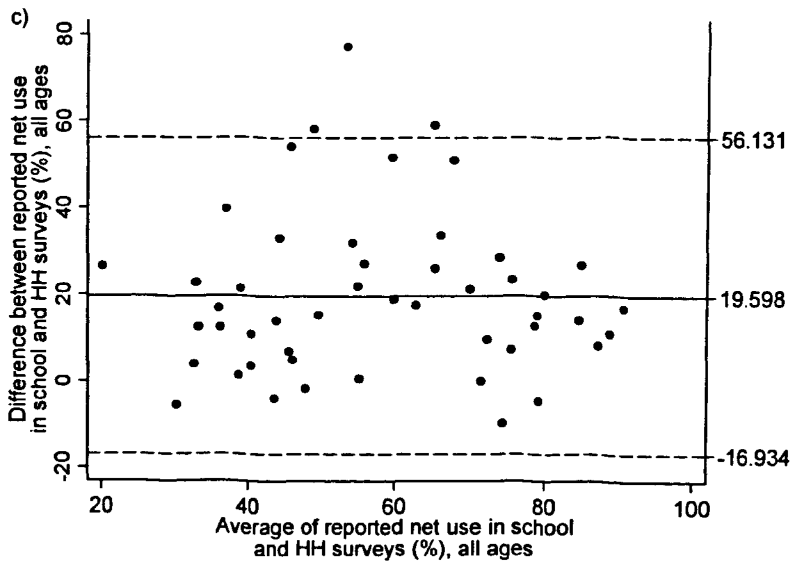
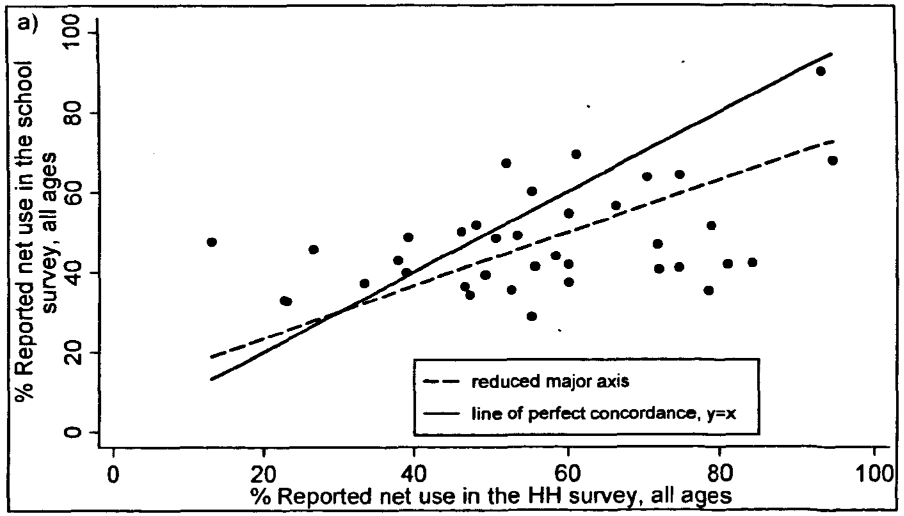
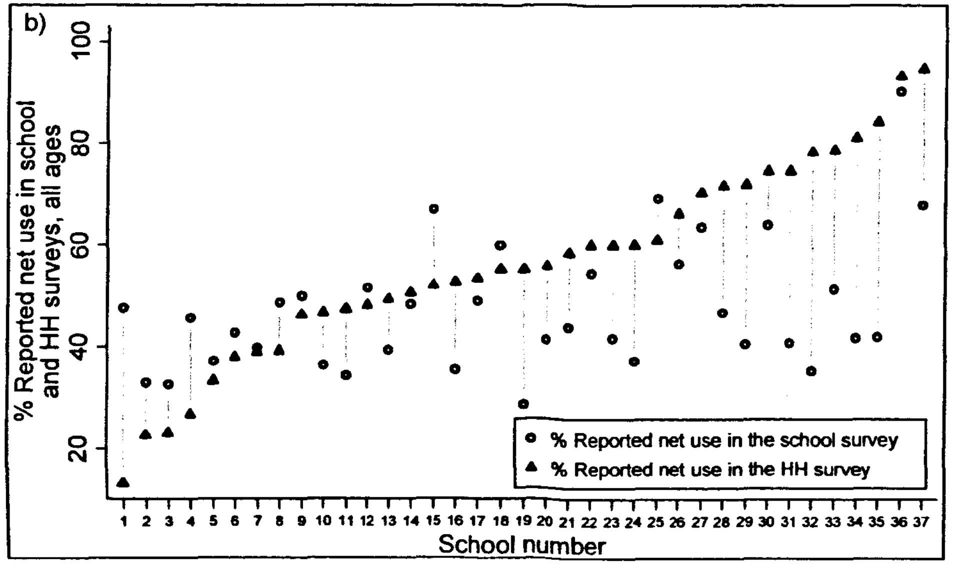
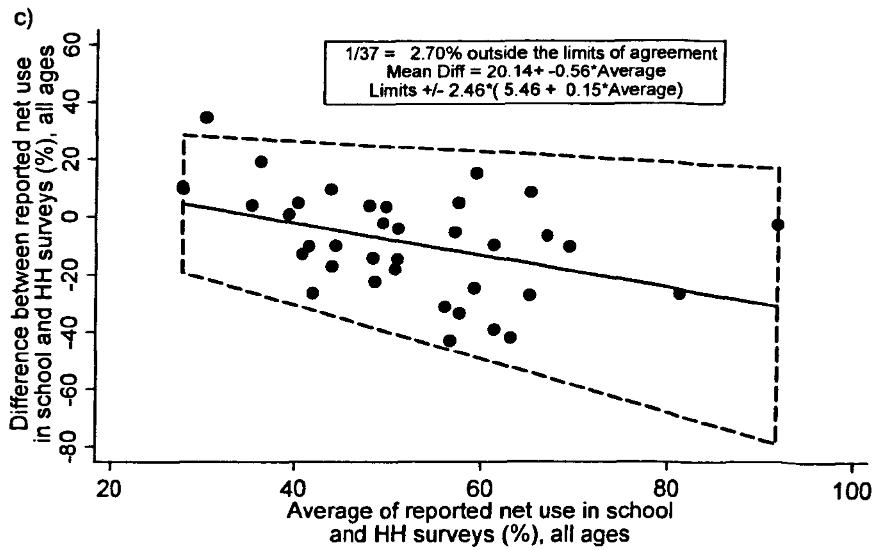


Figure 6.7: Relationship between reported net use estimates from school surveys and net use estimates in all ages in the community from household-based surveys in Kisii and Rachuonyo districts in Kenya in 2010. **a)** A scatter plot of the school and cluster level estimates. The dashed line represents the reduced major axis which shows the centre of the data. The solid diagonal line represents the line of perfect concordance, (y=x). **b)** A plot of the school and cluster level estimates with the solid vertical lines showing the magnitude of the differences between school and household estimates. **c)** Relationship between the difference (school estimates – HH estimates) and average reported net use estimates from school surveys and net use estimates in the community from household-based surveys. The solid line represents the mean and the dashed horizontal lines, difference and the 95% limits of agreement.







6.3.4. Congruence between national sample surveys

A total of 1,276 clusters from the household surveys were matched to the nearest school, and a total of 355 schools could be matched. There were minor differences between the national-level net use estimates from the school surveys and net use estimates for all ages from the national sample household surveys (Table 6.4). In the school surveys, 41.9% (95% CI: 39.6 – 44.2%) of children reported using nets the night before the survey while in the household-based survey 43.3% (95% CI: 41.9 – 44.6%) of the population was estimated to be using any net. The reported net use estimates from the school surveys were higher in Central, Coast, Eastern and in North Eastern and lower in Nairobi, Nyanza, Rift Valley and Western provinces compared to the net use estimates among children between the ages of 5 and 14 years in the household surveys (Table 6.4).

Table 6.4: Relationship between reported net use estimates from school-based surveys and estimates from national sample household surveys in Kenya. School-level net use estimates from the school surveys described in Chapter 2 are paired with estimates from national sample household surveys conducted in Kenya between 2008 and 2010. The household surveys include the 2010 Kenya Malaria Indicator Survey (2010 KMIS), the 2009 FinAccess survey by the Kenya Financial Sector Deepening programme (2009 FSD survey) and the 2008-2009 Kenya demographic health survey (KDHS 2008-09).

	National sample household surveys						School surveys	
Province	**Number of clusters/ persons examined**	**Reported net use, all ages[1]**	**Number examined, <5 years**	**Reported net use, <5 years[1]**	**Number examined, 5-14 years**	**Reported net use, 5-14 years[1]**	**Number of schools/ children examined**	**Reported net use, school children[1]**
Total	1,276/98,323	43.3 (41.9 – 44.6)	14,920	53.5 (51.9 – 55.1)	28,095	40.1 (38.6 – 41.6)	355 / 36,396	41.9 (39.6 – 44.2)
Central	178 / 11,595	29.9 (25.9 – 33.9)	1,360	40.6 (35.4 – 45.8)	2,859	29.4 (24.8 – 33.9)	22 / 2,387	37.1 (24.9 – 49.4)
Coast	153 / 13,071	54.1 (51.0 – 57.1)	2,145	64.3 (60.9 – 67.7)	3,631	54.2 (50.5 – 57.8)	65 / 6,892	59.0 (55.1 – 63.0)
Eastern	176 / 13,852	42.5 (39.0 – 46.1)	1,725	54.9 (50.6 – 59.1)	3,994	41.1 (37.3 – 45.0)	43 / 4,359	55.5 (49.5 – 61.5)
Nairobi	135 / 6,853	53.0 (48.8 – 57.3)	809	61.5 (56.1 – 66.9)	1,121	52.7 (47.2 – 58.3)	10 / 926	39.1 (27.8 – 50.3
North Eastern	68 / 6,869	35.6 (28.3 – 42.8)	1,106	40.9 (32.8 – 49.0)	2,630	34.0 (26.8 – 41.1)	26 / 2,576	45.7 (35.9 – 55.6)
Nyanza	191 / 15,495	52.8 (50.3 – 55.3)	2,628	62.8 (59.8 – 65.9)	4,488	45.3 (42.1 – 48.5)	62 / 6,302	38.7 (34.5 – 43.0)
Rift Valley	226 / 18,380	32.5 (29.6 – 35.4)	3,079	40.9 (37.3 – 44.4)	5,530	29.7 (26.5 – 32.9)	94 / 9,462	27.9 (24.5 – 30.9)
Western	149 / 12,208	47.9 (45.0 – 50.7)	2,068	59.2 (55.7 – 62.7)	3,842	39.3 (36.0 – 42.7)	33 / 3,492	37.8 (32.2 – 43.5)

[1] Proportions and 95% confidence intervals estimated using a multilevel random effects model adjusting for clustering at the school level in the school surveys, and at the cluster level in the household surveys.

6.3.5. Factors associated with incongruence

In the Tana and the Kisii/Rachuonyo surveys, mean age of the school children, household net coverage ratio, percentage of children under five in the cluster, prevalence of *Plasmodium* infection, malaria transmission zone and district were all associated with the magnitude and direction of the observed differences between the school and household survey net use estimates in the univariable model (Table 6.5).

Table 6.5: Factors associated with the differences in net use reports among the school children as reported in school surveys and net use reports among household members of all ages from household surveys (school – household estimates) in the Tana River/Delta and Kisii/Rachuonyo surveys.

	Univariable regression coefficients, (95% CI)	**LR test P value**	**Multivariable regression coefficients, (95% CI)**	**LR test P value**
School children mean age in years	-10.80 (-18.69 - -2.90)	0.007	-2.05 (-9.38 – 5.28)	0.551
HH net coverage ratio				
>4 people/net	1		1	
2-4 people/net	-13.63 (-22.74 - -4.51)		-8.50 (-18.82 – 1.82)	
<2 people/net	-37.17 (-48.01 - --26.33)	<0.001	-21.63 (-34.87 - -8.38)	0.003
Malaria infection prevalence by RDT				
0-0.9%	1		1	
1-4.9%	-4.40 (-20.63 – 11.84)		-3.60 (-18.42 – 11.21)	
5-39.9%	-22.88 (-32.90 – -12.85)		-13.50 (-26.33 - -0.66)	
>40%	-26.23 (-40.63 - -11.83)	<0.001	-5.85 (-24.24 – 12.55)	0.079
% of the population <5 yrs				
<15%	1		1	
15-25%	-24.72 (-33.57 - -15.87)		-13.43 (-24.27 - -2.60)	
>25%	-29.10 (-42.81 - -15.39)	<0.001	-12.12 (-28.78 – 4.54)	0.034
Malaria transmission zone				
Coastal	1		1	
Epidemic	-23.35 (--33.98 - -12.72)		5.06 (-13.45 – 23.47)	
Semi-Arid	7.79 (-3.09 – 18.67)	<0.001	10.34 (-2.71 – 23.39)	0.217
District				
Kisii/Rachuonyo	1			
Tana River/Delta	28.44 (20.49 – 36.38)	<0.001	Omitted [1]	

[1] District was omitted from the multivariable model due to collinearity with net coverage ratio.

In the multivariable model, only household net coverage ratio and percentage of children under five in the cluster were associated with the differences, after adjusting for age, prevalence of *Plasmodium* and malaria transmission zone. The mean difference was 22.23 (-22.23 (95% CI: -35.55 - -8.92) lower in school/cluster pairs where the household net coverage was less than two people for every net compared to school/cluster pairs where net coverage was more than four people for every net (Table 6.5).

In the national sample surveys, malaria infection prevalence, distance of the cluster sampled in the household survey from the school, province and malaria transmission zone were statistically significant predictors of the magnitude and direction of the difference between the school and household net use estimates in the univariable model (Table 6.6). In the multivariable model, however, only malaria transmission zone was statistically significant after adjusting for all the other factors. In the high transmission zone, the mean difference in net use was 20% lower (-20.11 (95% CI: -33.04 – -7.17) than the mean difference in the central low transmission zone (Table 6.6).

Table 6.6: Factors associated with the differences in net use reports among school children as reported in school surveys and net use reports among household members of all ages from household surveys (school – household estimates) in the nationwide school surveys reported in Chapter 2 and national sample household surveys conducted in Kenya between 2008 and 2010.

	Univariable regression coefficients, (95% CI)	**LR test P value**	**Multivariable regression coefficients, (95% CI)**	**LR test P value**
Malaria infection prevalence by RDT				
0-0.9%	1		1	
1-4.9%	-3.37 (-9.75 – 3.01)		-1.76 (-8.43 – 4.90)	
5-39.9%	-9.79 (-15.59 - -3.99)		-0.65 (-8.38 – 7.07)	
>40%	-19.92 (-27.78 - -12.06)	<0.001	-2.57 (-14.17 – 9.02)	0.931
Distance from school				
0-4.9 km	1		1	
5-9.9 km	-3.58 (-9.22 – 2.06)		-2.89 (-8.50 – 2.72)	
10-19.9 km	-1.20 (-7.53 – 5.12)		-3.84 (-10.26 – 2.58)	
>20 km	*10.05 (2.52 – 17.58)*	<0.003	1.99 (-6.25 – 10.23)	0.349
Province				
Central	1		1	
Coast	-1.19 (-10.75 – 8.37)		-11.70 (-27.98 – 4.58)	
Eastern	6.12 (-3.82 – 16.06)		3.32 (-7.11 – 13.76)	
Nairobi	-14.16 (-29.59 – 1.27)		-14.75 (-31.02 – 1.52)	
North Eastern	0.55 (-10.11 – 11.21)		-7.48 (-23.53 – 8.56)	
Nyanza	-18.76 (-28.21 - -9.31)		-3.08 (-17.47 – 11.30)	
Rift Valley	-9.22 (-18.31 - -0.13)		-6.07 (-16.44 – 4.30)	
Western	-15.34 (-25.93 - -4.75)	<0.001	-0.22 (-15.38 – 14.93)	0.070
Malaria transmission zone				
Central	1		1	
Coastal	1.88 (-4.74 – 8.51)		10.48 (-5.00 – 25.96)	
Epidemic	-8.77 (-14.42 – 3.11)		-6.59 (-15.17 – 2.00)	
High Transmission	-21.29 (-27.50 - -15.07)		-20.11 (-33.04 – -7.17)	
Semi-Arid	3.98 (-2.78 – 8.50)	<0.001	5.19 (-6.59 – 16.97)	0.016

6.4. Discussion

Disease control requires up-to-date information on disease burden and intervention coverage. In malaria control, school malaria surveys can potentially be used to provide data on the epidemiology of malaria and the coverage of interventions such as ITNs, however, the usefulness of ITN reports by school children is based on the ability of children to accurately report ITN use. The aim of this Chapter therefore, was to assess the congruence between net use reports by school children and net use reports from household-based surveys. At the individual level, children were more likely to over-report than under-report net ownership and net use. The over-reporting resulted in overestimation of the school-level net use estimates in almost all schools in the Tana River/Delta surveys and in schools where the household-based cluster-level reported net use was low in the Kisii/Rachuonyo surveys.

School children have been shown to reliably estimate infection prevalence and intervention coverage. In schistomiasis studies for example, school children's reports on blood in urine have been shown to be reliable indicators of schistosomiasis prevalence when compared with parasitological surveys[6, 8, 15]. Other studies such as the Ugandan ITN study described earlier[3] and the Ivermectin coverage studies in Uganda[4] and Nigeria[5] have also shown that school children can reliably report intervention coverage. Although the results from this study suggest that school children over-reported net use, we hypothesize that behavioural factors at the household-level may have affected reporting at the household-based surveys. In Tana River and Tana Delta, the surveys were part of the study described in Chapter 2, assessing the impact of LLIN distribution through schools. We therefore believe the households could have underreported net coverage and use hoping to benefit from the LLIN distribution. In the Kisii/Rachuonyo surveys, the school surveys under-reported net use in areas where the net use estimates from the household surveys were high and over-reported in areas where net use estimates from the household surveys were low. In the Kisii/Rachuonyo surveys therefore, the households could have under-reported net use in the areas of low bed net coverage and where there was perceived need for more nets and over-reported in areas where net coverage was high but the nets were not in use especially by the *school age group*. Several studies have shown that behavioural factors such as sleeping arrangements are likely to affect net use by the school aged children[16, 17]. Studies in western Kenya, have shown that older children are most likely to sleep in a non-sleeping areas and not on a bed are therefore least likely to use a net even when there are extra nets in the household. Other studies malaria endemic areas in Madagascar and Sierra Leone showed that over 20% of children between the ages of 6-15 years did not sleep under an ITN in households where there was an ITN hanging over their sleeping spaces[18]. Such findings may explain the discrepancies in reported net use between school surveys and household surveys, with school children honestly reporting non-use while the parents assuming use of hang nets. However, although many studies have reported differences between net ownership and use, more in-depth qualitative investigations of reported versus actual net use are warranted.

The study further explored the factors that were associated with the magnitude and the direction of the differences between the reported net use at the school level and net use estimates among all ages in the household surveys. In the Tana River/Delta and the Kisii/Rachuonyo survey, the net use estimates from the school surveys were likely to be lower than the net use estimates from the household surveys, in clusters where the reported net/person ratio was high and where the reported population of children under the age five years was high. In the national sample surveys, school surveys were likely to underestimate net use in the high transmission regions. This observation could be explained by the previous LLIN delivery strategies in Kenya, which largely targeted only children under the age five years and pregnant women. For example in 2006 the government of Kenya distributed LLINs through a free mass distribution to children under five, to rapidly increase net use among children under the age of five years[9, 19, 20]. In the mass distribution, the nets were distributed to all the districts in Nyanza and Western provinces, due to the high malaria transmission intensity while in the other provinces the nets were only distributed to the malaria-prone districts. This could explain the differences in net use between the school aged children as observed in the school surveys, and the estimates from the household surveys due to the high coverage in children under five in Nyanza and Western provinces. However such inequitable net coverage could be addressed by programmes aimed at universal coverage, and therefore potentially improve the congruence between the school and household survey net use estimates. The National Malaria Strategy in Kenya[21] supports universal coverage to all persons at risk and last year the Kenyan government through the national malaria control programme distributed bed nets in all malaria endemic districts with the aim of achieving universal coverage (one net for every two people). Further studies are required to assess the comparability of reported net use in school surveys and household surveys after the mass distribution aimed at universal coverage.

This study has several limitations. First, as highlighted earlier, the study design in the Tana River/Delta surveys would have influenced reporting of net ownership and use in the household surveys. This highlights one important issue, that although household surveys are the mainstay for assessing net use because the presence of a net can be ascertained, such surveys may not able to ascertain the absence of a net. Secondly, the temporal lag between the school surveys and the national sample surveys may potentially reduce the observed congruence between the surveys. However in the three year period no mass distribution of bed nets was done in Kenya and therefore no large changes in net coverage were expected.

In conclusion, although this study does not provide conclusive results on the use of schools as a proxy to monitor community level net use, school surveys could still be useful as countries move into universal coverage of bed nets to *all populations at risk*. However further in-depth studies are warranted to compare reported net use and actual use at the household level as well as the congruence between school children's reports and household surveys as countries move into universal coverage.

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Chapter 7 : Summary and discussion

In the last decade there has been significant progress in malaria control in Africa with increased funding[1,2] and access to malaria control interventions[3,4] and a concomitant reduction in disease burden[4,5]. However, millions of people at risk of malaria still remain unprotected[3]. Studies across varied malaria transmission settings show that school-age children are the age group least protected by malaria control interventions such as ITNs[6], despite harbouring the highest proportion of infections regardless of the transmission intensity[7]. However, very little is known about the epidemiology of malaria in school children to effectively guide control. This thesis therefore was aimed at evaluating the usefulness of school-based malaria surveillance to define the epidemiology and burden of malaria among school children in Kenya, and evaluating the impact of school-based approaches to control malaria in different transmission settings in Kenya. This chapter provides a summary of the findings and their implications, and also identifies areas of future work.

7.1. Summary of findings

School based surveys could be a useful tool for planning malaria control by defining the epidemiology and burden of malaria in school children and their surrounding communities. However, although school malaria surveys formed an important part of malaria reconnaissance during the pre-eradication period (see Chapter 1), there are very few contemporary examples of school-based malaria surveys in malaria endemic countries. Chapter 2 presented the main results of the first ever nationwide school malaria survey in Kenya and discussed the methodological issues encountered in the implementation of the surveys. The results demonstrated that the prevalence of

Plasmodium infection among school children in Kenya was low at 4.6%, but there was marked geographical variation in infection prevalence across the different malaria ecologies in Kenya. Similarly, there was marked geographical variation in patterns of anaemia and reported net use. These results highlight the need for rapid scaling-up of malaria control interventions, such as ITNs, in the school-age population, but that interventions should be geographically targeted to achieve maximum impact due to the variation in the levels of *Plasmodium* infection and anaemia. Operationally, the results demonstrated that school malaria surveys provide an easy, rapid and inexpensive platform for malaria surveillance but the variation in the prevalence of *Plasmodium* infection may have implications for the reliability of malaria diagnostic strategies used in school malaria surveys due the variation in parasite density. Furthermore, it was unclear if school surveys could be useful in monitoring intervention coverage in the wider community – these issues were considered in subsequent chapters.

The design of a geographically targeted malaria control package should not only be informed by the distribution and prevalence of infection, but also the potential effectiveness of available control interventions. Using the data from national school survey, an analysis of the potential risk factors for *Plasmodium* infection and anaemia was undertaken in Chapter 3. The results suggested that although reported net use was associated with reduction in the odds of *Plasmodium* infection among all children in the coastal malaria transmission zone and among males in the western highlands epidemic zone, there was no statistical evidence of a protective effect in all other malaria transmission zones, including in the lakeside high transmission zone. The lack of an effect in the high transmission zones may have been explained, in part, by the high infection prevalence and the low reported net use. Moreover, despite anaemia being most common in the coastal and semi-arid zones, analysis suggested that *Plasmodium* infection was not a statistically significant risk factor for anaemia in those zones, but reported net use was associated with reduction in anaemia in the coastal zone. Such findings suggest that other aetiologies of anaemia, such as malnutrition and helminth infections, may be important contributors of anaemia in the coastal and semi-arid zones[8].

Chapter 4 presented results from a cluster randomised trial in conducted in two districts in the coastal and semi-arid malaria transmission zones. The trial was designed to evaluate the impact of long lasting insecticide treated nets (LLINs) distributed through schools on *Plasmodium* infection, anaemia and reported net use among school children. The results suggested that LLINs distributed through school increased net use among children in the intervention schools highlighting the role that schools can play in supporting community-wide control of malaria. However, the trial results did not provide evidence of LLINs reducing the prevalence of *Plasmodium* infection or anaemia. Such findings support the findings from Chapter 3 that suggest other factors may play an important role in the aetiology of anaemia in the coastal and semi-arid zones.

Collectively, the results in Chapters 2, 3 and 4 provide useful guidance for the planning of malaria control among school children in Kenya. The high prevalence of *Plasmodium* infection and low rates of net use in the high transmissions and epidemic zones highlight the need for increasing access to malaria control interventions in these zones. As demonstrated in Chapter 3, low levels of net use in areas of high transmission is unlikely to be associated with substantial reductions in malaria transmission and efforts to increase net usage, coupled with other control approaches such as indoor residual spraying, are needed in order to have maximal impact[9, 10]. To rapidly increase net use in the high transmission districts, the existing school system can be used as a complementary entry point for bed net distribution, as demonstrated in Chapter 4. In addition, the existing school system can also be used to deliver health messages on net use and prompt treatment[11-14].

Effective malaria control programmes need to be based on reliable and up-to-date data on epidemiology of malaria and intervention coverage. The experience from the national school malaria survey reported in Chapter 2 indicated that school surveys provided an inexpensive, easy and rapid platform for malaria surveillance. The use of school surveys is however predicated on the assumptions that school surveys can provide reliable data on infection levels and on intervention coverage. Therefore, chapters 5 and 6 set out to test these assumptions by assessing the reliability of malaria rapid diagnostic tests (RDTs) used in school malaria surveys as well as the reliability of school children's reports on bed net use as a proxy for community level coverage. Analysis in Chapter 5 showed that although RDTs yielded high false positivity at the individual level, they are still reliable in classifying localities to according to infection prevalence in very low (<1%) and high (>40%) transmission settings. Importantly, the results demonstrated that RDTs offer an affordable approach in school-based surveys, especially when coupled with more accurate diagnostic strategies such as PCR.

Besides providing epidemiological data, school surveys could be useful tool for monitoring intervention coverage, both among school children themselves and within their communities[15]. In order to assess the usefulness of school surveys in monitoring bed net use, Chapter 6 analysed the congruence between school children's reports on net use from school surveys and reports from household heads in household-based surveys. The analysis indicated that although the school surveys overestimated net use at the school/cluster level, the overestimation was generally consistent and it was unclear whether, in fact, school children's reports or their parents' reports were more reliable, as there was no way of truly validating estimates. In terms of estimating net use at a sub-national level, estimates from school and household surveys aggregated at a provincial level were comparable for all provinces except for the high transmission provinces of Nyanza and Western. Thus, although the results were inconclusive about the reliability of school-based reports to monitor net use in the community, schools surveys could still be a useful proxy for community level coverage as many countries achieve universal and uniform coverage in the population sub-groups.

7.2. Future directions

The analysis presented in this thesis has provided an understanding of the epidemiology and burden of malaria in Kenyan school children and offered novel insights into the usefulness of school-based approaches to malaria surveillance and control. Despite the promising role of school malaria surveys there are still several issues that need to be investigated further. First, the usefulness of schools to provide data on *Plasmodium* infection which are representative of the wider community will depend on a number of factors, including, level of school enrolment, level of absenteeism and sampling procedures[7] and the influence of such factors need to be evaluated in future studies. Second, the data provided in this thesis forms an important basis for future schools malaria surveys in Kenya. However, the school malaria surveys presented in this thesis were undertaken over a long period of time (2008 – 2010) and the results could have been affected by temporal changes in malaria transmission due to seasonality and use of control interventions. Malaria seasonality in Kenya follows the bimodal rainfall pattern with peak transmission periods just after the start of the long rains between April and August and shortly after the start of the short rains from October to December. Such seasonality may affect the observed infection prevalence depending the timing of the surveys, and further affect the classification of schools and districts into the prevalence categories (<1%, 1-4.9%, 5-39.9% and >40%) highlighted in Chapter 5. Appendix 1 presents the distribution of malaria seasons in Kenya and Appendix 2 presents the relationship between the rainfall patterns and timing of the surveys in the different malaria transmission zones in Kenya. Most schools were sampled during the short rains season or shortly after. In the central malaria transmission zone where transmission is very low or transmission does not occur, most the schools were sampled September and November 2009 in the short rains season and the prevalence and subsequent classification may not have been affected by the timing of the surveys (Appendix 2.1a and b). Similarly, most schools in the high transmission and epidemic zones were also sampled just after the long rains or shortly after the start of the short rains (Appendix 2.3 and 2.4). Although a few districts were sampled in the dry season of between January and March 2010 in the high transmission areas, the observed prevalence would have been higher but it may not affect the classification of schools into prevalence categories due to the high school level prevalence. In contrast, the observed prevalence estimates in the Coastal and semi-arid transmission zones may have been an underestimation. Most schools were sampled in dry months (Appendix 2.2a and b, and appendix 2.5a and b) and the observed low prevalence may have been due to the timing of the surveys. Additionally, as highlighted in Chapter 3, the school surveys were conducted between 2-3 years after the last mass distribution of bed nets in 2006 and the observed prevalence may have captured a rise in prevalence due to poor quality nets. The above factors have to be considered while interpreting the results presented in this thesis.

Third, this thesis demonstrated that RDTs provided a cheap and reliable tool for malaria diagnosis but the analysis did not consider how the performance of RDTs varies in different transmission settings, which may have implications for cost-effectiveness of diagnostic approaches. Fourth, additional studies are warranted in different transmission settings of the effectiveness of school-based distribution of bed nets. Fifth, the results are inconclusive about the use of schools to monitor bed net coverage and, as highlighted in Chapter 6, further qualitative studies would be needed to explore the reliability of reported net use in the community and the factors that influence accurate reporting. Finally, there is need for further studies on the congruence between school and household surveys net use estimates as countries move into universal coverage.

In conclusion, this thesis has provided a contemporary example of a large scale school malaria survey in Africa and provided data on the epidemiology and burden of malaria in school children in Kenya. The thesis has also demonstrated the potential for school-based control in reducing the burden of malaria, but additionally highlighted how malaria interventions should be geographically targeted and included into an integrated school health package that also includes deworming, iron supplementation and school feeding. Finally, this thesis has provided insights into usefulness of school-based surveillance, which may be a useful tool for malaria surveillance as transmission declines[7, 16]. The challenge now is to build upon these results to identify the cost-effective and optimal approach to school-based malaria surveillance and control in the different transmission settings across Africa.

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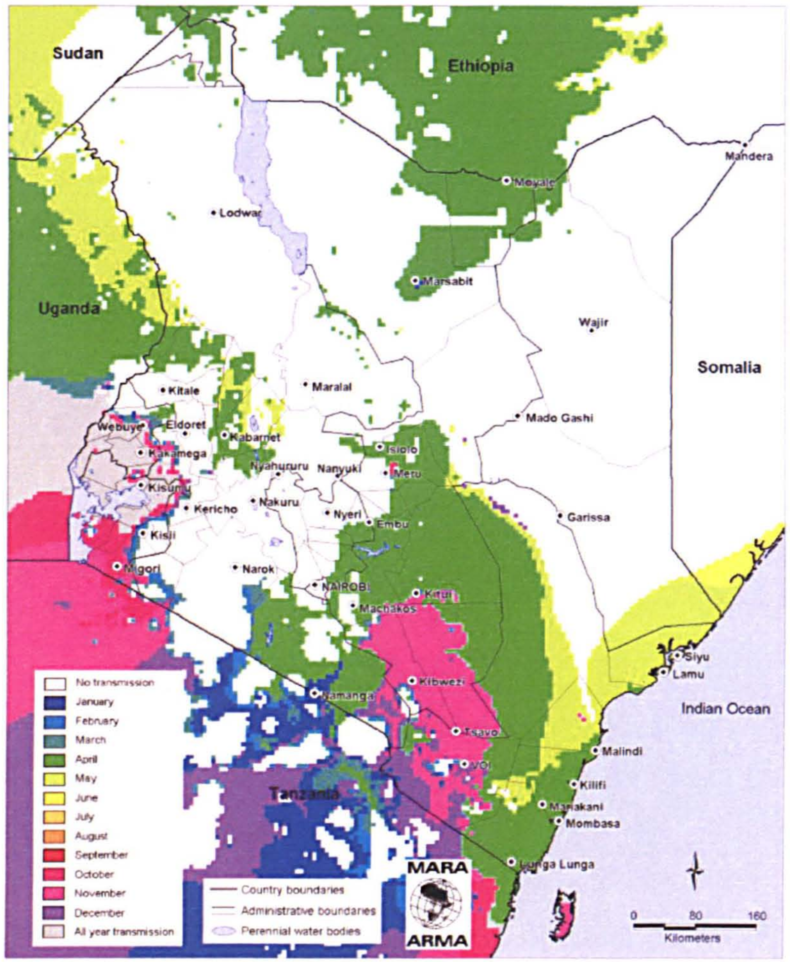
Appendix 1: Malaria seasonality in Kenya.

Appendices 1a-c represent the months of peak malaria seasons and the duration of the malaria seasons in Kenya. Maps adapted from the MARA website:

http://www.mara.org.za

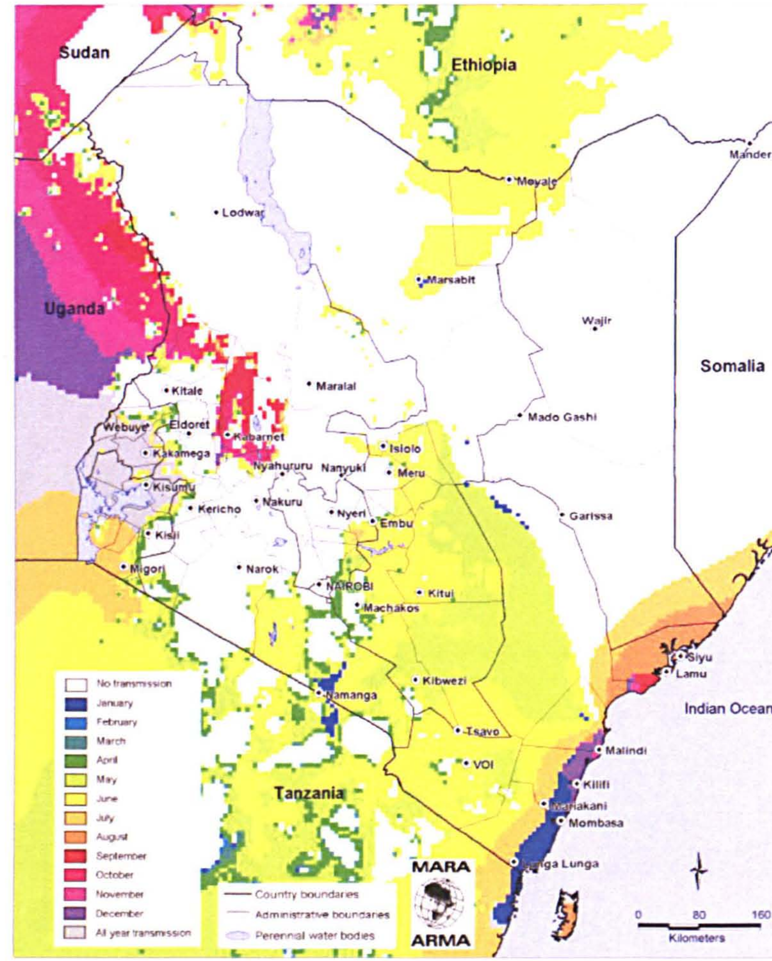
Appendix 1a: The first and the last month of the first malaria transmission season

Kenya: First Month of the First Malaria Transmission Season



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001. Medical Research Council. PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute; Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM)
Malaria seasonality model: Tanser, F et al. 2001. Paper in preparation
Topographical data: African Data Sampler, WRI: http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm

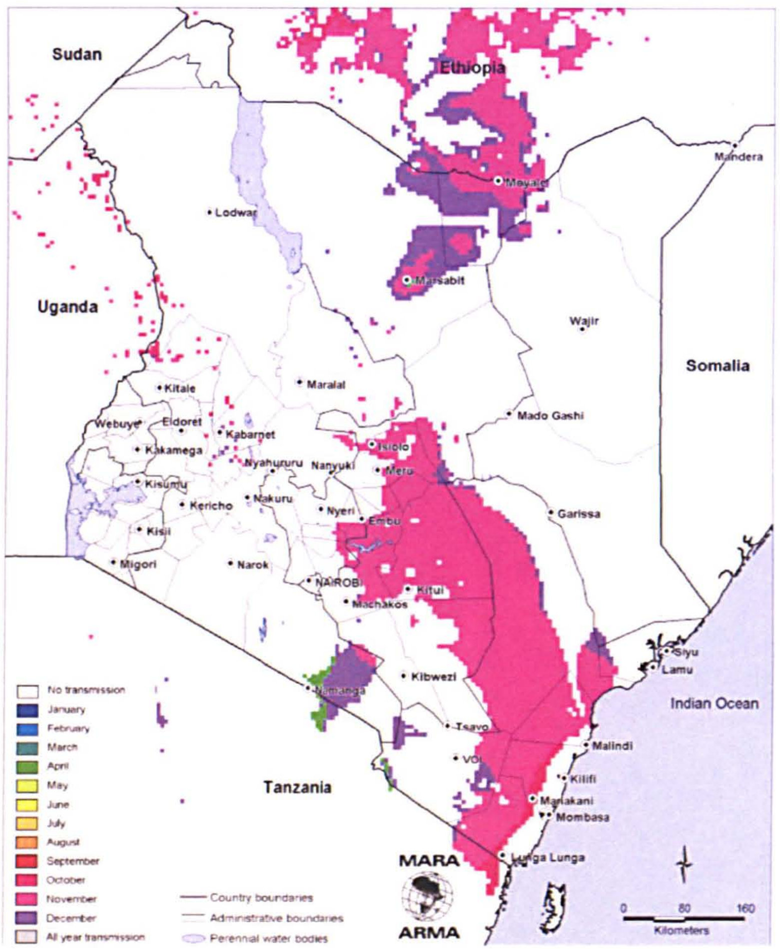
Kenya: Last Month of the First Malaria Transmission Season



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001. Medical Research Council. PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute; Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM)
Malaria seasonality model: Tanser, F et al. 2001. Paper in preparation
Topographical data: African Data Sampler, WRI: http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm

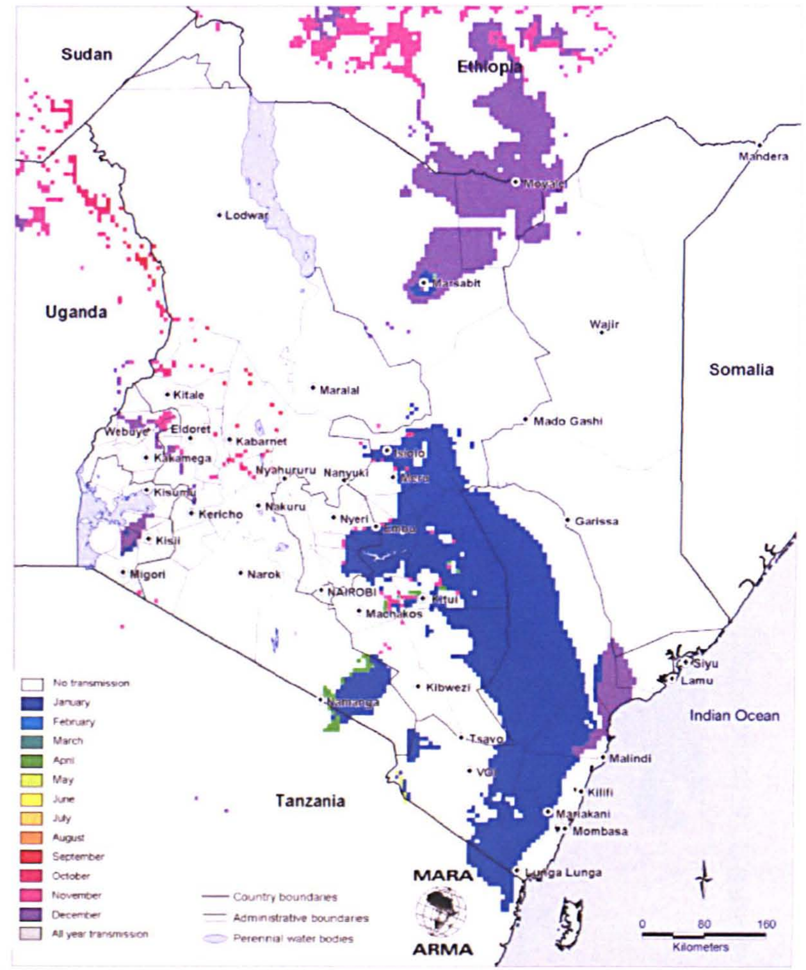
Appendix 1b: The first and the last month of the first malaria transmission season

Kenya: First Month of the Second Malaria Transmission Season



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001. Medical Research Council, PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute; Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM).
Malaria seasonality model: Tanser, F et al. 2001. Paper in preparation.
Topographical data: African Data Sampler, WRI, http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm

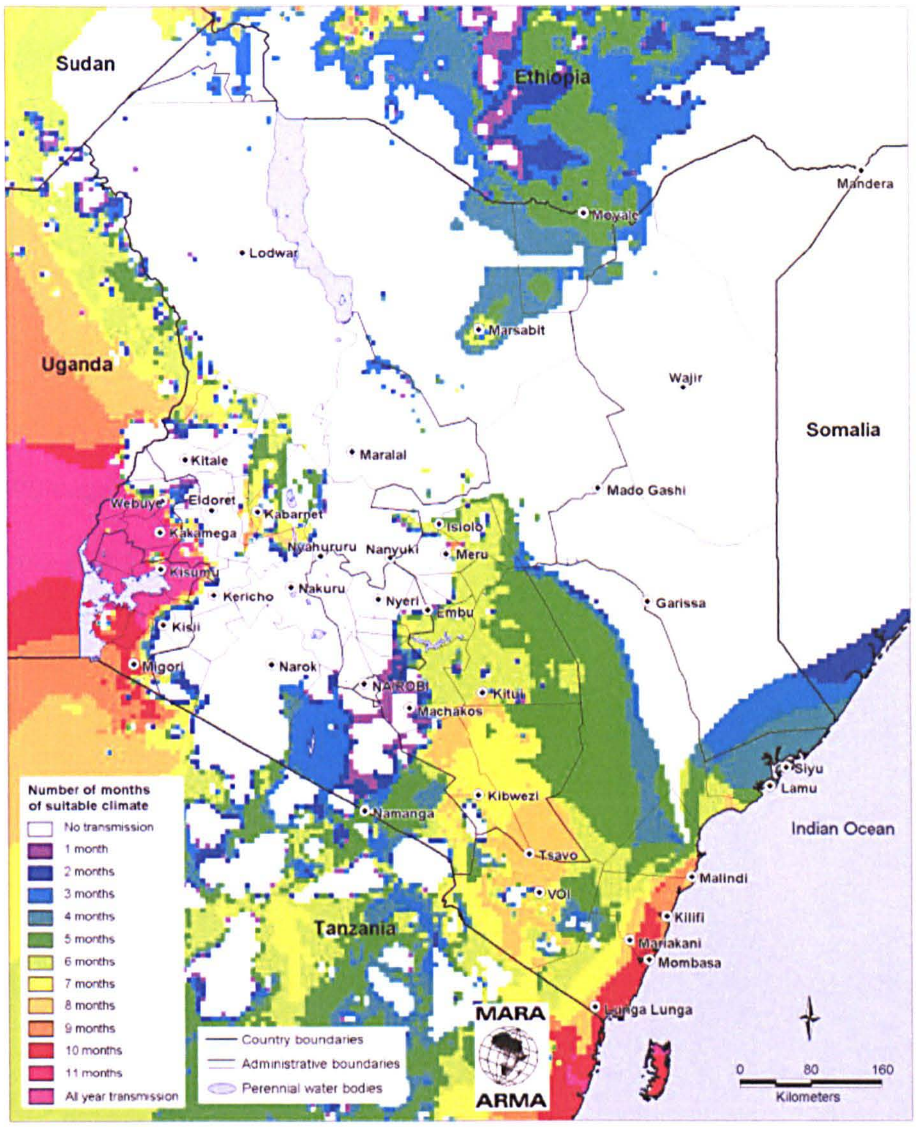
Kenya: Last Month of the Second Malaria Transmission Season



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001. Medical Research Council, PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute; Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM).
Malaria seasonality model: Tanser, F et al. 2001. Paper in preparation.
Topographical data: African Data Sampler, WRI, http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm

Appendix 1c: Duration in months of the malaria transmission season in Kenya

Kenya: Duration of the Malaria Transmission Season



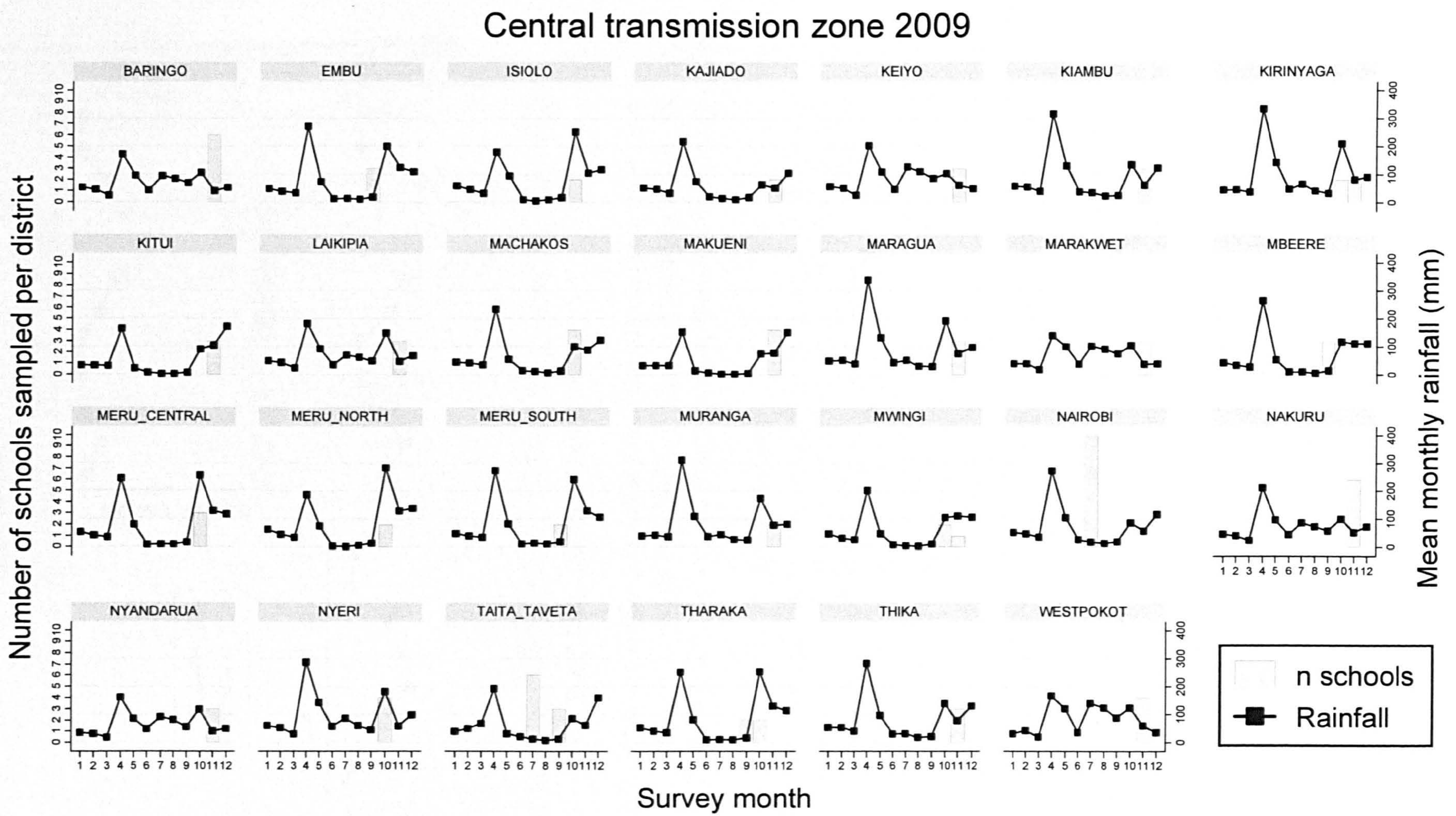
This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001. Medical Research Council. PO Box 17120, Congella, 4013. Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute; Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM)
Malaria seasonality model: Tanser, F et al. 2001. Paper in preparation
Topographical data: African Data Sampler, WRI. http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm

Appendix 2: Relationship between school surveys timing and the rainfall patterns in the study areas in the years 2008 - 2010.

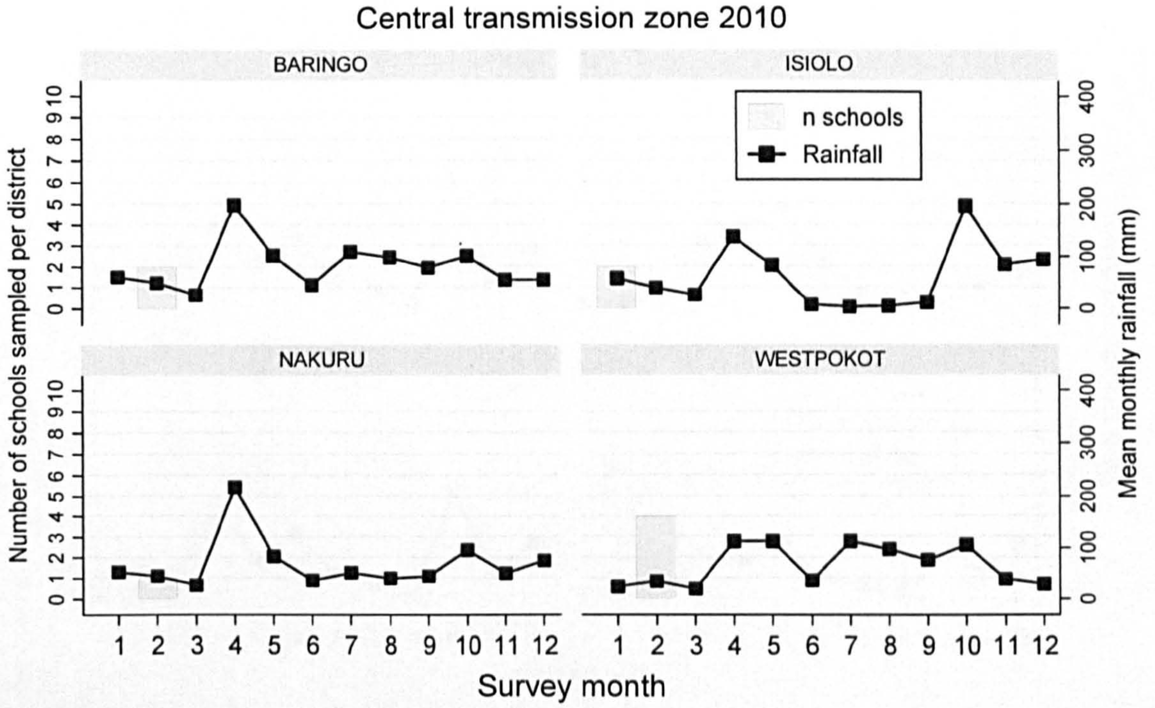
Rainfall data:

The mean rainfall estimates for each month the year of survey were extracted for the s survey districts from the University of East Anglia Climatic Research Unit (CRU), Global precipitation dataset (http://www.cru.uea.ac.uk/data). The CRU time series version 3.10 dataset used, provides mean monthly rainfall estimates between 1901-2009 on high-resolution (0.5x0.5 degree) grids based on monthly archived estimates from over 19,800 weather stations around the world. The data was kindly provided by Caroline Kabaria of KEMRI/Wellcome trust and I was responsible for the analysis.

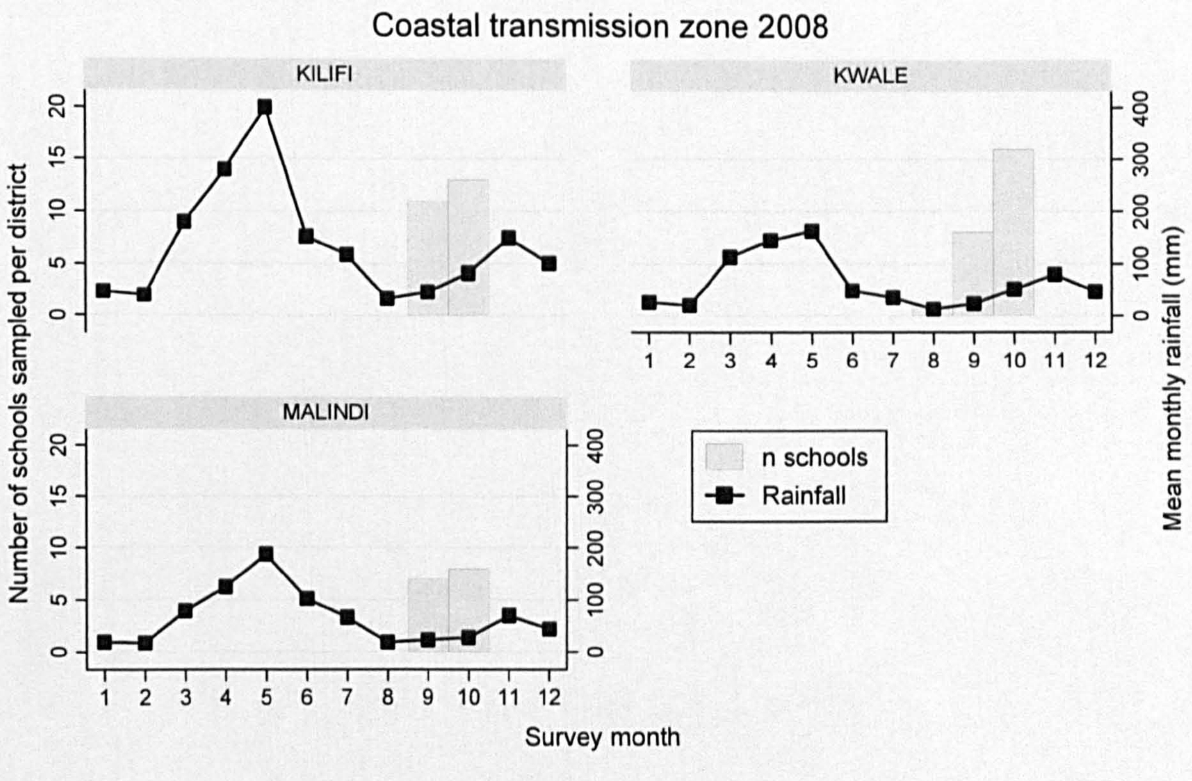
Appendix 2.1a: Relationship between school surveys timing and the rainfall patterns in the central low transmission zone in 2009. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



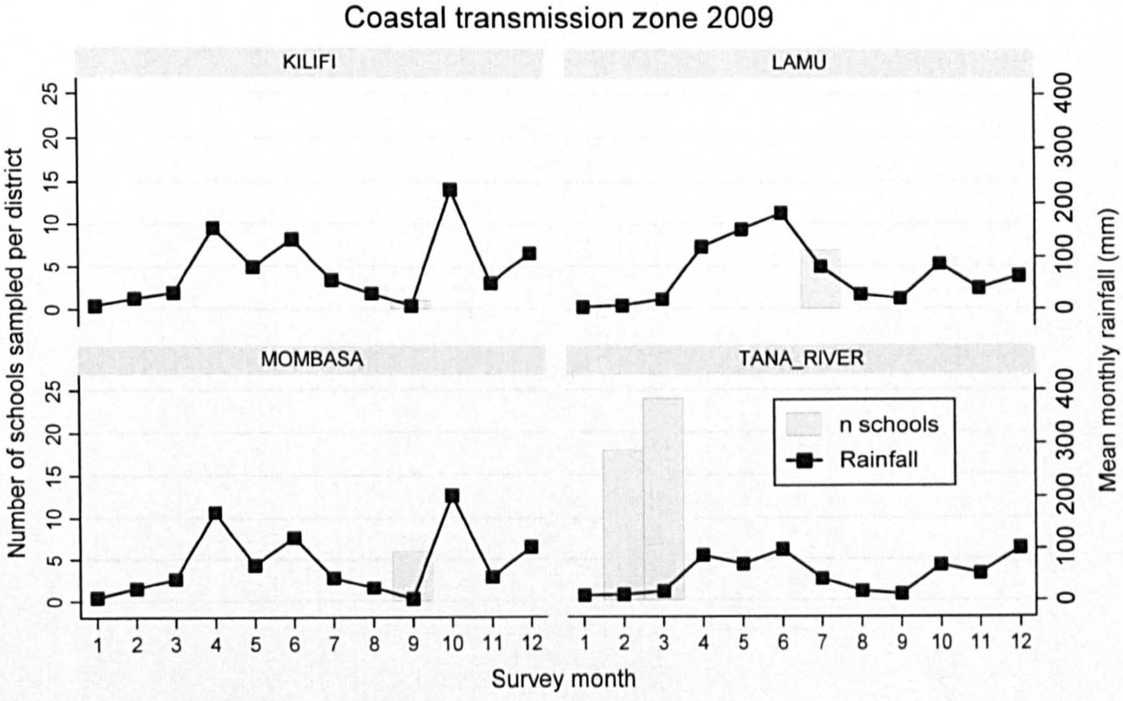
Appendix 2.1b: Relationship between school surveys timing and the rainfall patterns in the central low transmission zone in 2010. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



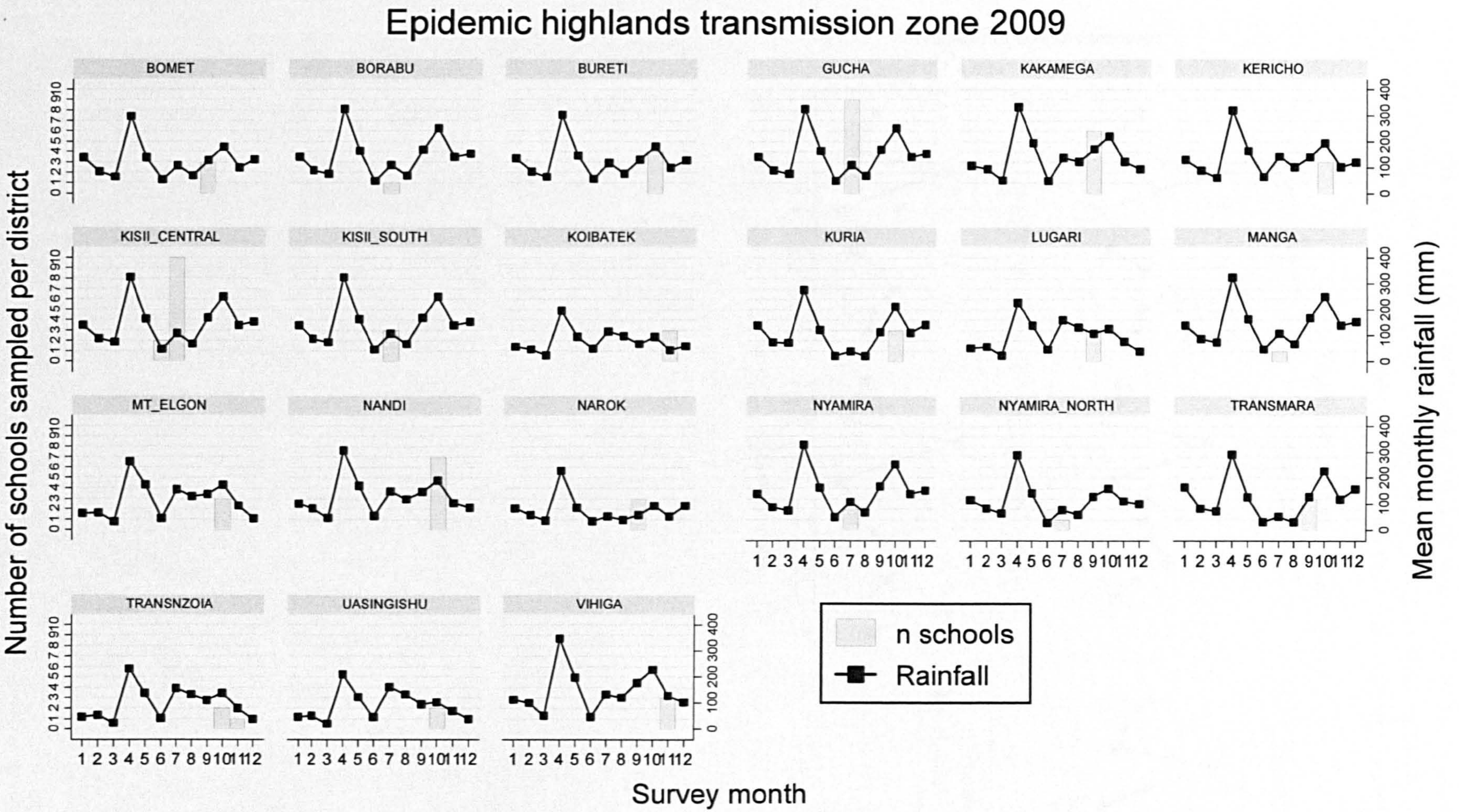
Appendix 2.2a: Relationship between school surveys timing and the rainfall patterns in the coastal transmission zone in 2008. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



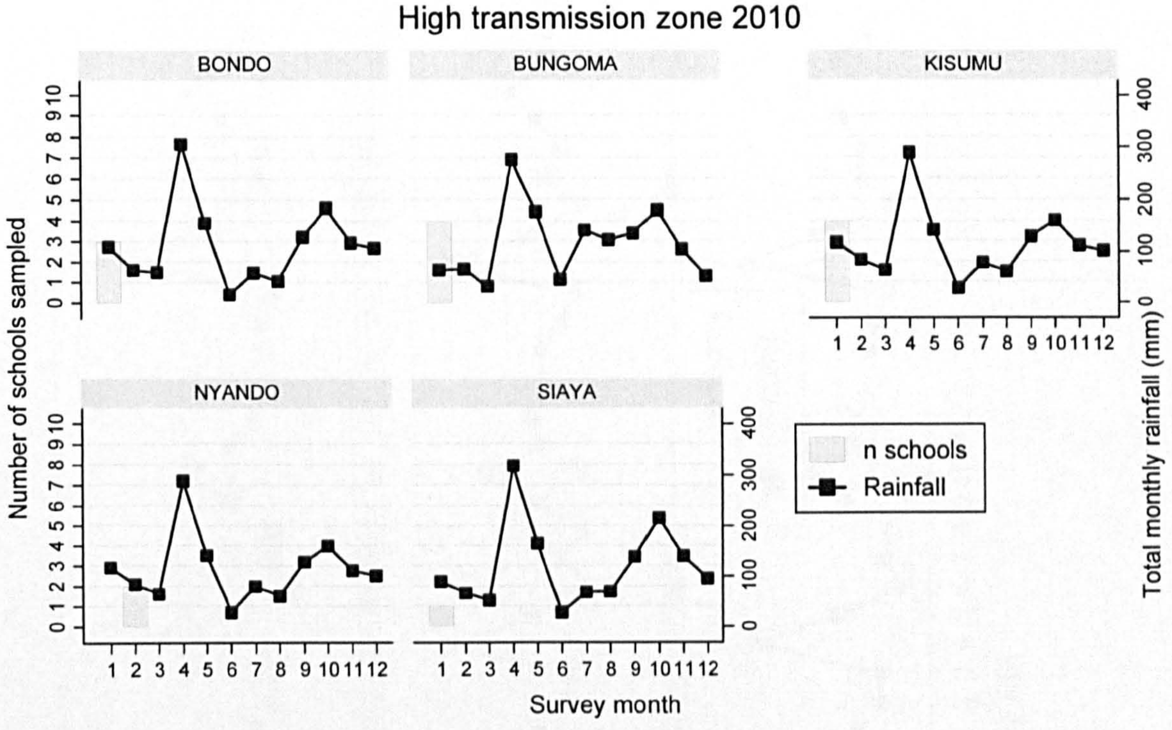
Appendix 2.2b: Relationship between school surveys timing and the rainfall patterns in the coastal transmission zone in 2009. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



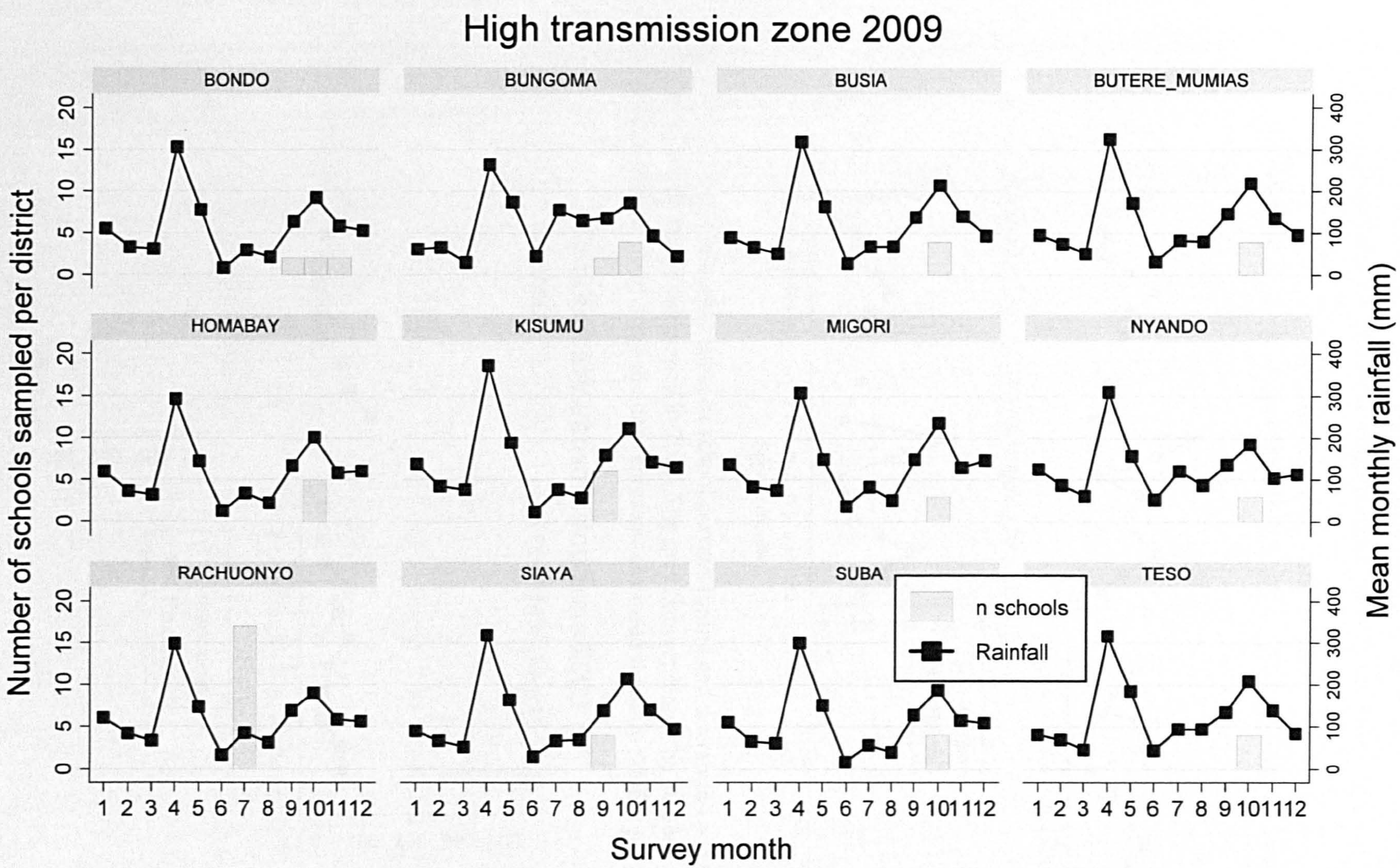
Appendix 2.3a: Relationship between school surveys timing and the rainfall patterns in the epidemic highlands transmission zone in 2009. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



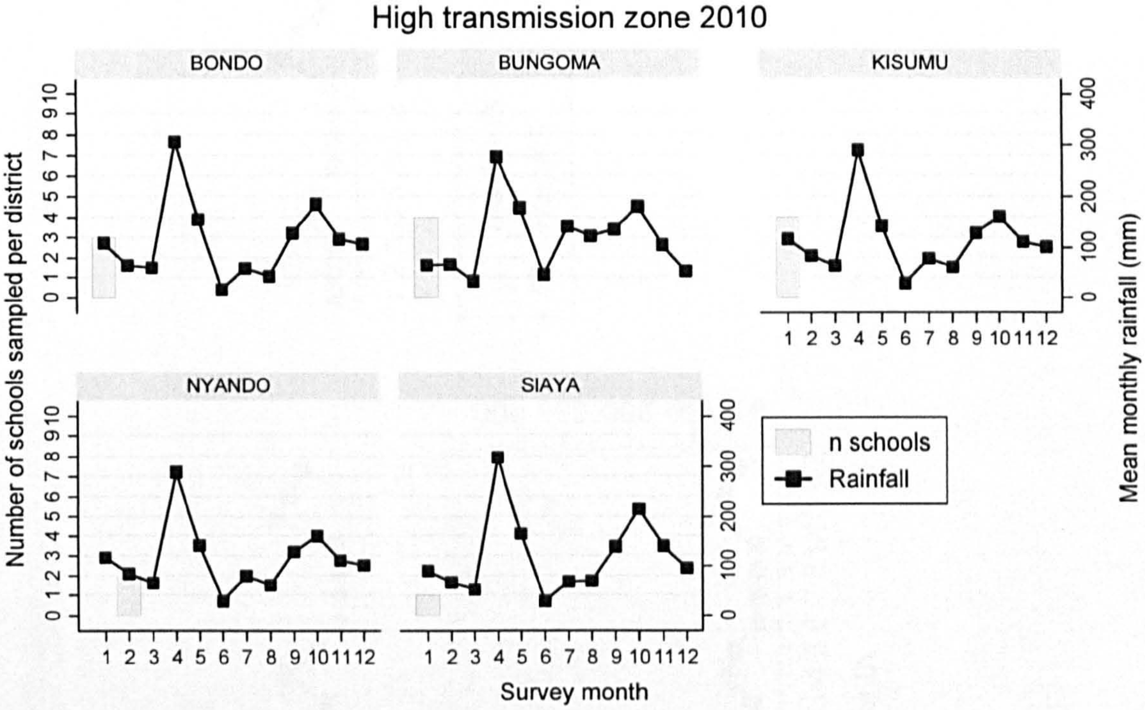
Appendix 2.3b: Relationship between school surveys timing and the rainfall patterns in the epidemic highlands transmission zone in 2010. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



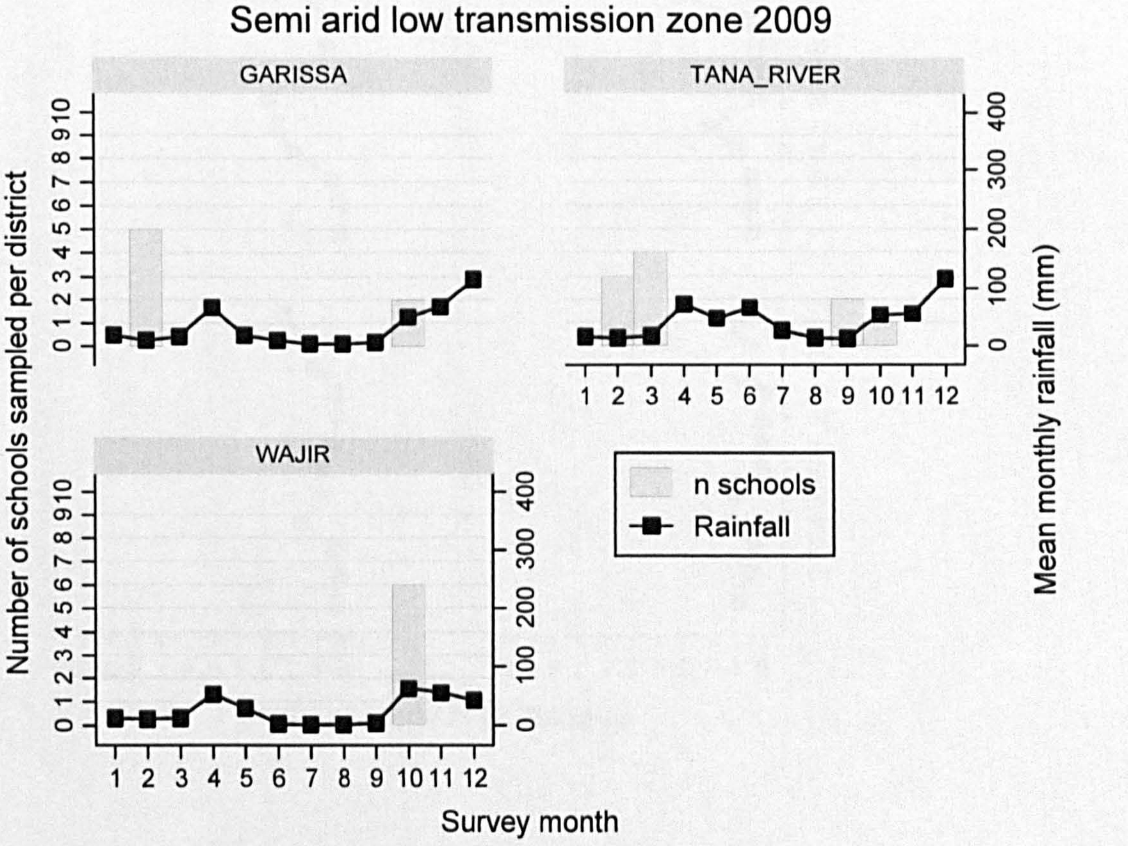
Appendix 2.4a: Relationship between school surveys timing and the rainfall patterns in the high transmission zone in 2009. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



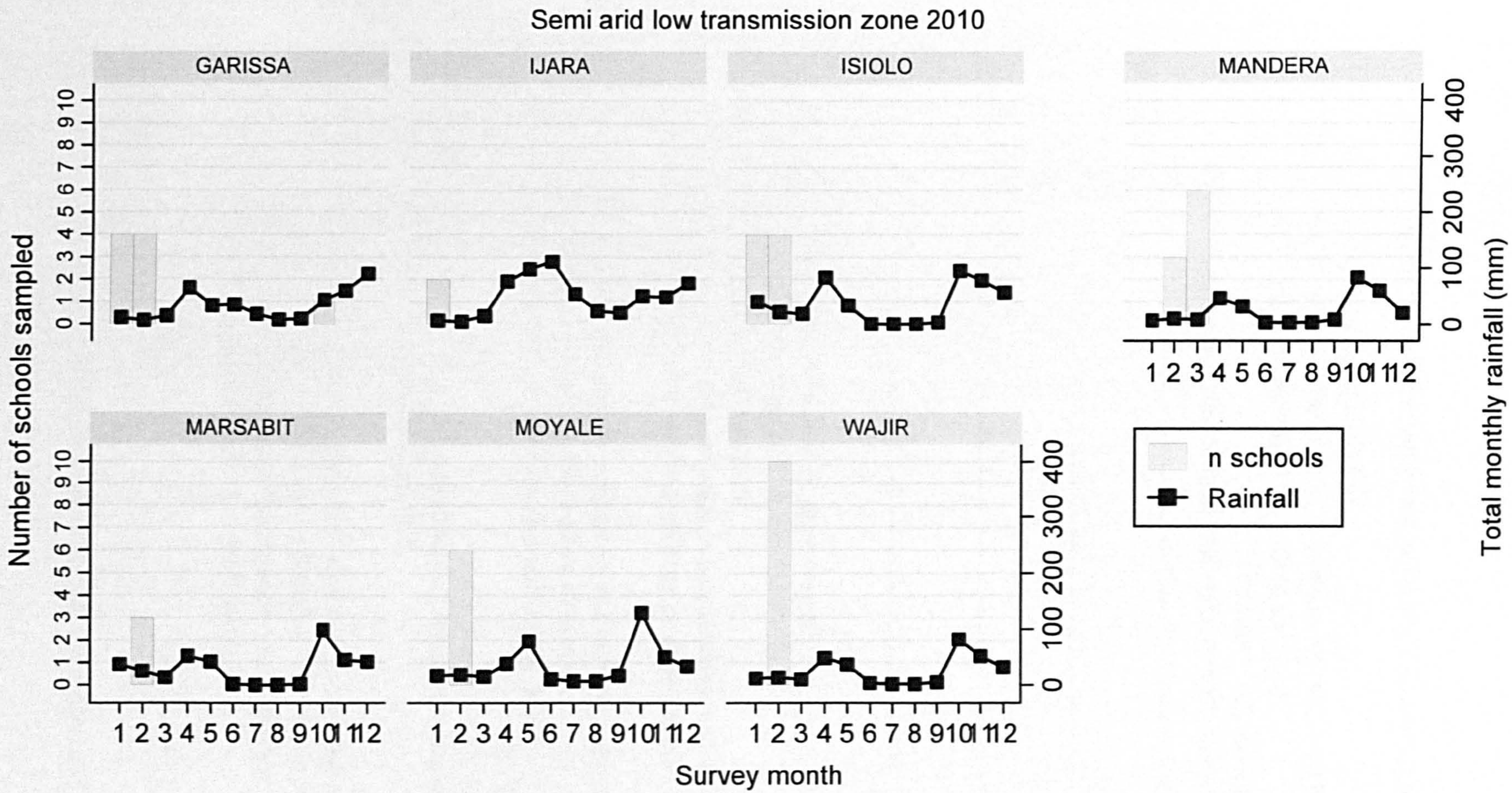
Appendix 2.4b: Relationship between school surveys timing and the rainfall patterns in the high transmission zone in 2010. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



Appendix 2.5a: Relationship between school surveys timing and the rainfall patterns in the semi arid low transmission zone in 2009. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



Appendix 2.5b: Relationship between school surveys timing and the rainfall patterns in the semi arid low transmission zone in 2010. The grey bars represent the number of schools sampled per district and the line represents the mean monthly rainfall per district.



Appendix 2: Research papers cover sheets

Cover sheet for each 'research paper' included in a research thesis: Chapter 2

1. For a 'research paper' already published
   1.1. Where was the work published? Malaria Journal, volume 9
   1.2. When was the work published? October 2010
   1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
   ___N/A___

   1.3. Was the work subject to academic peer review? Yes
   1.4. Have you retained the copyright for the work? No
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published? N/A
   2.2. List the paper's authors in the intended authorship order
   N/A

   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press N/A

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)
   I participated in the study design and coordinated data collection. I undertook all the data cleaning and analysis, and wrote the draft manuscript.

Candidate's signature

Supervisor or senior author's signature to confirm role as stated in (3)

Cover sheet for each 'research paper' included in a research thesis: Chapter 3

1. For a 'research paper' already published
   1.1. Where was the work published? Tropical Medicine and International Health, Volume 17, issue 7
   1.2. When was the work published? July 2012
      1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
      __N/A____
   1.3. Was the work subject to academic peer review? Yes
   1.4. Have you retained the copyright for the work? No
      If yes, attach evidence of retention
      If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published? N/A
   2.2. List the paper's authors in the intended authorship order

   __N/A____

   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press N/A

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   I participated in the study design and coordinated data collection. I undertook all the analysis and wrote the draft manuscript.

Candidate's signature _

Supervisor or senior author's signature to confirm role as stated in (3)

Cover sheet for each 'research paper' included in a research thesis: Chapter 4

1. For a 'research paper' already published
   1.1. Where was the work published?
   ____N/A____________________________
   1.2. When was the work published?
   ____N/A____________________________
   1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
   ____N/A____
   1.3. Was the work subject to academic peer review?
   ___N/A________________________
   1.4. Have you retained the copyright for the work? __N/A___
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published? _PLOS ONE______________________
   2.2. List the paper's authors in the intended authorship order

   Caroline W Gitonga, Tansy Edwards, Peris N Karanja, Elizabeth Allen, Cassian Mwatele, George Okello, Joseph Kiambo Njagi, Antony Kanjah, Robert W Snow and Simon J Brooker

   2.3. Stage of publication –Undergoing revision from peer reviewers' comments

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   I participated in the study design and coordinated data collection. I also undertook all the data analysis and wrote the draft manuscript.

Candidate's signature
Supervisor or senior author's signature to confirm role as stated in (3)

Cover sheet for each 'research paper' included in a research thesis: Chapter 5

1. For a 'research paper' already published
   1.1. Where was the work published? American Journal of Tropical Medicine and Hygiene, Volume 87, Issue 6
   1.2. When was the work published? December 2012
      1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
      N/A
   1.3. Was the work subject to academic peer review? Yes
   1.4. Have you retained the copyright for the work? No
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published?
   N/A
   2.2. List the paper's authors in the intended authorship order
   N/A
   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press N/A

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   I participated in the study design, coordinated data collection and supervised microscopy slide reading. I undertook all the data analysis and wrote the draft manuscript.

Candidate's signature
Supervisor or senior author's signature to confirm role as stated in (3)